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Section of Anæsthetics

President—JOHN GILLIES, C.V.O., M.C., M.R.C.P.Ed., F.R.C.S.Ed., F.F.A. R.C.S.

[*February* 1, 1952]

Distribution and Fate of Anæsthetic Drugs

By C. A. KEELE, F.R.C.P.

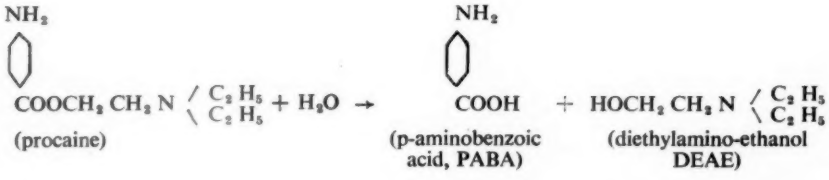
IN discussing the fate of anæsthetic drugs I shall be dealing mainly with compounds which are broken down in the body, and I shall not refer to the gases and volatile anæsthetics.

The distribution of drugs in the body is, of course, dependent on the normal activity of the circulation and respiration, and the actions will depend on the concentrations reached in the different compartments of the body fluids. Finally the uptake of drugs by the cells will be determined by such factors as lipoid solubility and reduction of surface tension, although cellular function can be profoundly influenced by substances with very low lipoid solubility, such as acetylcholine and tubocurarine, which combine specifically with receptors on the cell surface.

The study of the metabolism of drugs can only be properly carried out when sensitive methods, chemical or biological, are available to determine the concentrations of the parent compound and its metabolic products in the fluids and tissues of the body. It is also most important to know something concerning the pharmacological activity of the products of drug metabolism so that one may assess the significance of these products in relation to the changes in physiological function.

FATE OF PROCAINE IN THE BODY

Procaine is probably the most rapidly metabolized drug known, there being in the plasma (and in the liver) a special enzyme called "procaine esterase" (Kisch, Koster and Strauss, 1943) which hydrolyses the substance to its components, p-aminobenzoic acid (PABA) and diethylamino-ethanol (DEAE).



(procaine) (p-aminobenzoic acid, PABA) (diethylamino-ethanol DEAE)

In man it has been shown by Brodie, Papper and Mark (1950*b*) that 90% of the PABA and 33% of the DEAE so formed appear in the urine within twenty-four hours. Only small amounts of PABA occur in the free or acetylated forms, most of the PABA being conjugated with glycine to form p-aminohippuric acid and some combines with glucuronic acid (Tabor *et al.*, 1951). The products of metabolism of DEAE are not known.

The rate of hydrolysis of procaine by plasma is very high and Brodie *et al.* (1950*b*) found that *in vitro* the enzyme in human plasma completely destroyed 5 mg./litre of procaine in about five minutes. The safety of intravenous procaine infusions depends on this speedy breakdown, since both toxic effects and therapeutic actions (e.g. analgesia or depression of cardiac excitability) are due to the unchanged procaine and not to the products of breakdown. For reduction of excitability of heart muscle about 30 times as much PABA as is formed from an effective dose of procaine has to be given. *In vivo*, procaine infusions produce only very low plasma concentrations of the unchanged drug. For example, Brodie *et al.* (1950*b*) found that after intravenous infusion in man of 2 grammes of procaine during 105 minutes the procaine plasma level never exceeded 0·2 mg./l., while the concentration of PABA rose to 13 mg./l. and that of DEAE to 2·8 mg./l.

Burgen and I (1948) have studied the plasma procaine levels in cats immediately following rapid intravenous injections of procaine and also during short infusions of relatively large doses of the drug. In both cases the plasma procaine levels fell rapidly after the drug administration ended. For example, after injection of 30 mg. of procaine in 30 seconds, the plasma level fell from 77 mg./l. to 7·5 mg./l. in five minutes. This fall could be due to:

(1) Dilution, resulting from diffusion of the drug from the blood stream into the tissue fluids of the body.

(2) Fixation of unchanged procaine by the tissues.

(3) Destruction in blood and tissues.

(4) Excretion.

Excretion of unchanged procaine in the urine (about 3% of the total) was quite inadequate to explain the rapid fall in plasma procaine concentration. Calculations showed, too, that even if the procaine had been uniformly distributed throughout the total body water, this dilution could only account for less than one-third of the procaine which had disappeared from the blood. It was therefore clear that the injected procaine had been extensively fixed by the tissues, or speedily destroyed: the simultaneous increase in plasma PABA concentration in fact showed that the disappearance of procaine from the blood was mainly due to its breakdown. At the end of an infusion of 80 mg. of procaine in thirteen minutes the plasma level fell from 65 mg./l. to 25 mg./l. during the next five minutes. In this case the drug would have been quite uniformly distributed throughout the body fluids during the infusion and the subsequent rapid fall in plasma level must have been almost entirely due to destruction of procaine.

We also tried to determine what part such organs as the kidney and liver play in the destruction of procaine. The kidney certainly eliminates only a minute fraction of injected procaine via the urine, but it might still destroy the substance; however, in experiments in which we tied off the renal pedicles we found no evidence that this was the case. On the other hand, there was good evidence that in eviscerated cats (with no portal blood flow) the liver played a significant part in the destruction of procaine, since occlusion of the hepatic artery during an infusion caused the plasma procaine level to rise sharply.

These experiments have been described to illustrate how the fate of a drug may be followed when its detoxication products are known and when sensitive chemical methods are available for determination of the concentrations of the parent compound and its derivatives in the body fluids. However, where one is dealing with such a rapidly destroyed substance it is impossible to determine its concentration in the various organs and tissues of the body. The barbiturates, which are all much more stable than procaine in the body, will be used to illustrate this aspect of distribution.

The Barbiturates

Studies on the distribution and fate of the barbiturates have in the past been handicapped by inadequate chemical methods of estimation. The difficulties are discussed in the review by Maynert and Van Dyke (1949), who point out that most of the methods cannot distinguish between the depressant parent compound and its inactive metabolites. The improved techniques which have recently been developed to overcome this problem have provided more accurate and detailed information which has changed our ideas in some important respects.

Distribution.—In discussing the distribution of the barbiturates it is convenient to deal first with the brain, and it is appropriate to begin by referring to the work of Das (1940), who studied the speed of onset of action of a number of barbiturates when they were administered intravenously to mice. He found that the median hypnotic doses of thiopentone and hexobarbitone caused sleep in one to two minutes, whereas the corresponding doses of pentobarbitone and barbitone took five and twenty-two minutes respectively. It is interesting to note that Shideman and Gould (1951) found that with thiopentone equilibrium between blood and brain was attained one minute after injection. It is also

significant that the oil/water coefficient of the rapidly acting thiopentone is about 4·7, whereas that of the slow-acting barbitone is 0·214. Using reliable chemical methods of determination Butler (1950) has further shown that the uptake of barbitone by the brain is much slower than that of the rapidly acting Hexethal (Ortal). Butler, in the work just mentioned, and Maynert and Van Dyke (1950), in experiments on dogs to which they administered barbitone containing ^{15}N, have shown that there is no evidence of selective concentration of barbitone in any particular regions of the brain.

Plasma Levels of Thiopentone after Intravenous Injection

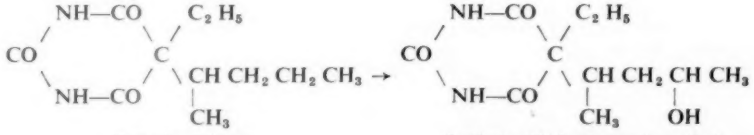
Brodie *et al.* (1950*a*) found that after intravenous injection of 0·4 gramme of thiopentone in two minutes the initial plasma concentration was 28 mg./l. During the first few minutes after injection the plasma level fell rapidly, and subsequently more slowly. After infusions lasting up to fifty minutes the plasma level fell slowly and only about 10–15% of the drug was destroyed per hour. This suggests that the brevity of action of intravenous thiopentone when given as a single dose is due to redistribution rather than detoxication of the drug. After infusions or repeated injections thiopentone is relatively long-acting owing to its rather slow rate of destruction.

Thus the initial high uptake of thiopentone by the brain accounts for the rapid induction of anæsthesia, and the subsequent rapid recovery is correlated with the fall in plasma level associated with the speedy redistribution of the drug throughout the body. The sites of redistribution have been studied only recently (Brodie *et al.*, 1950*a*). Liver and kidney contain somewhat higher concentrations than occur in plasma, but two to three hours after injection the highest concentrations are found in samples of body fat, in which levels five to ten times those of plasma, may be found. Equilibrium between blood and fat is reached only one to two hours after injection (Shideman and Gould, 1951), probably owing to the poor blood supply to this tissue. The implications of this redistribution are important, since the fat constitutes a sort of reservoir in which the thiopentone will be stored and subsequently released to be detoxicated relatively slowly by oxidation. The fat thus behaves as a buffering mechanism which will influence slightly the intensity, and much more the duration of action of thiopentone. The more fat there is in the body the more efficient should this buffering action be, and the briefer should be the effect of a single intravenous injection of thiopentone. It is therefore very important to take into account the variations in fat content of the body which have been reported by McCance and Widdowson (1951). They estimated the percentage of fat in normal men to be 7·2 to 22·4% of the body-weight and in normal women 12·6 to 28·5% of the body-weight. It would be most interesting to correlate the percentage body fat with duration and intensity of action of thiopentone.

Metabolism of Barbiturates

The metabolic changes undergone by the barbiturates have been reviewed recently by Maynert and Van Dyke (1949). After allowance has been made for the inadequate methods of determination which have been used in the past the following statements may be made concerning a few of the most important members of this group. Barbitone is excreted unchanged, up to 90% of the administered drug appearing in the urine. Phenobarbitone is excreted unchanged in the urine to about 25% of the amount given, the remainder being detoxicated, perhaps partly in the kidney. With both these long-acting drugs the excretion is slow, lasting several days. The barbiturates which act rapidly and briefly, e.g. pentobarbitone, hexobarbitone and thiopentone, are almost completely destroyed in the body, only traces of unchanged drug appearing in the urine. There is little evidence that significant breakdown of the barbiturate ring occurs, and the suggestion that the sulphur atom of this thiobarbiturate is replaced by oxygen is not supported by studies made with thiopentone containing ^{35}S.

The most important metabolic change undergone by the three short-acting compounds mentioned above is oxidation of the side-chain. Thus pentobarbitone is converted to 5-ethyl: 5(3-hydroxy-1 methylbutyl) barbituric acid.



Pentobarbitone

5-ethyl : 5(3-hydroxy-1 methyl-butyl) barbituric acid

The longer side-chains are much more easily oxidized than the shorter ones. The cyclo-hexenyl ring of hexobarbitone is also oxidized (Bush and Butler, 1941), and thiopentone is converted to a carboxylic acid (COOH) derivative. All these products of oxidation lack the central nervous depressant actions of the parent compounds.

Sites of Metabolism of Barbiturates

The extensive earlier work on the part played by the liver in the breakdown of the barbiturates will not be reviewed here. It may now be said that recent work by Walker and Wynn Parry (1949), Shideman *et al.* (1947), and Shideman and Gould (1951) has shown that all the shorter-acting barbiturates are detoxicated in the liver. *In vitro* liver slices, and even cell-free preparations of liver tissue inactivate these barbiturates (Gould and Shideman, 1951).

Detoxication may perhaps occur also in other tissues, such as the kidney and brain, but there is little precise information on this point.

Distribution and Fate of *d*-Tubocurarine

d-Tubocurarine is a quaternary ammonium compound with negligible lipoid solubility. It is therefore to be expected that it will not easily penetrate the cells of the body. Indeed Mahfouz (1949) found that in man the drug was distributed in a volume of fluid equal to that of the plasma volume, the maximum concentration being about 4 μg./ml. at the time of full paralysis. No tubocurarine was found in the red blood cells. Buller and Young (1949) have shown that tubocurarine does not cross the placenta in rabbits, a result which agrees with the clinical finding that the drug may be given for Cæsarean section without the danger of paralysing the new-born child. It also seems likely that with the usual doses of tubocurarine little or no penetration into the central nervous tissue occurs, though Salama and Wright (1950) have shown that injections of the drug into the cerebrospinal fluid causes powerful stimulant effects, including convulsions.

In mice, Mahfouz found that 60% of tubocurarine was inactivated in the body within four hours, perhaps largely in striated muscle. There is no evidence that liver or kidney are significant sites of destruction, and hepatic or renal damage does not contra-indicate the administration of tubocurarine.

Methonium Compounds

The methonium compounds such as decamethonium (C10) and hexamethonium (C6) are quaternary ammonium substances with very low lipoid solubility. One would therefore expect them to be distributed in the plasma and interstitial fluid, without entering the cells of the body. Like tubocurarine they will, of course, become attached to the surface of cells on which they act, e.g. the motor end-plates in the case of decamethonium and the ganglion cells of the autonomic nervous system in the case of hexamethonium. Also like tubocurarine, decamethonium does not cross the placental barrier (Young, 1949).

Methonium compounds are not metabolized in the body and after injection they are almost entirely excreted in the urine (Zaimis, 1950; Milne and Oleesky, 1951). The drugs pass out via the glomeruli and are neither excreted nor reabsorbed by the cells of the renal tubules. It is therefore important to realize that if the arterial blood pressure is reduced to less than 50 mm.Hg (when glomerular filtration ceases), a drug such as hexamethonium will no longer be excreted even though renal blood flow is well maintained as the result of the vasodilatation induced by the drug.

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Clinical Section

President—HAROLD EDWARDS, C.B.E., M.S.

[*January* 11, 1952]

Four Cases Illustrating Aspects of Leprosy.—R. G. COCHRANE, M.D.

The following 4 cases were presented, 2 of which illustrated typical tuberculoid cases (major lepride). Case III illustrated what is generally accepted as the atypical, or borderline group (atypical lepride).

The two tuberculoid cases were as follows:

I. Male, aged 10. (*Dr. J. R. Owen's case.*) *Not illustrated.*

5.2.51: Admitted to hospital.

History.—Six weeks ago injured left hand which had become swollen and painful. Four weeks ago was not feeling fit. Two weeks ago swelling of his hand occurred and he had an influenza-like illness which was prevalent in the family at the time.

Previous medical history.—Nephritis 1947, when in India. Six months prior to admission, pain in right leg and stiffness in walking.

Family history.—Nothing of note.

Condition on admission.—Complexion slightly dusky. Lesion on left hand and right leg; indurated swelling of ulnar border and hypothenar region of left hand, extending to and involving left fifth finger and ring finger; tender on pressure. Also tenderness in region of ulnar nerve. Raised, dusky red area, not tender, on posterior aspect of right thigh and calf. A few flesh-coloured papules on ulnar side of right wrist and a few reddish papules over lower part of both legs. Lesions on left hand and right leg showed sensory disturbances.

Wassermann reaction: 2+.

Progress and treatment.—17.3.51: Patient was placed on Sulphetrone, 0·5 gramme twice daily, orally. This was increased to 0·5 gramme thrice daily on 9.4.51. There was slight cyanosis and the dose was reduced. Sulphetrone was discontinued on 19.6.51 and thiacetazone, 25 mg. daily, was given. On 16.7.51 this was increased to 25 mg. twice daily.

July 1951: Seen by R. G. C. who pointed out that there was no gross improvement and, further, the left ulnar nerve was greatly enlarged and thickened, indicating considerable damage. ? nerve abscesses.

21.8.51: Mr. G. G. Farrington exposed the left ulnar nerve and excised the sheath. There were three nerve abscesses. Wound healed well. Patient given diaminodiphenylsulphone, starting at 50 mg. a week (25 mg. twice a week) and increasing slowly to the dose at present taken—300 mg. twice a week. Considerable clinical improvement has taken place.

Mr. G. G. Farrington: *Comment on Case I.*

In August 1951 I explored this boy's ulnar nerve. For a length of more than 6 in. it was nearly half an inch thick, slightly nodular, tense, almost elastic in consistence and of a dusky red colour; much œdema fluid exuded from the tissues. The nerve sheath was stripped off with a striking relief of tension and in a few minutes the cyanotic hue had changed to a healthier red. Three nodular swellings were incised and found to be intraneural abscesses. To the surgeon the picture was that of a swollen œdematous nerve being strangled by its own sheath. There was no tension on the nerve in any position of the elbow and anterior transposition was not required. In spite of the appearance of acute inflammation healing was by first intention. Subsequently there has been some improvement in the paralysis presumably because of relief of tension. Many neurones must have been destroyed and recovery is likely to be incomplete.

Opportunities for the surgical treatment of leprosy in this country may not be quite so rare as we think. Dwyer, F. C. (1951, *J. Bone Jt. Surg.*, 33B, 604) recently reported two similar though rather more chronic cases and I operated three years ago on a tumour of the ulnar nerve with cyst formation closely resembling his description, and possibly also a chronic form of neural leprosy. The possibility should certainly be remembered when dealing with obscure tumours of the peripheral nerves, especially ulnar and peroneal. If permanent damage is to be prevented early operation is essential. This is particularly important when Sulphetrone is given as this agent causes intense local reaction and sometimes precipitates the onset of paralysis.

II. Male, aged 29. (*Dr. S. P. Hall-Smith's case*, Figs. 1 and 2.)

History.—July 1951: Sudden development of eruption affecting face, trunk and limbs. During same period experienced severe pain in left leg and weakness in left foot.

One month prior to this admitted Royal Sussex County Hospital, Brighton, with suspected appendix, which was later diagnosed as gastro-enteritis. Discharged from hospital after one week. One week before admission to hospital given sulphonamides "for 'flu" and developed morbilliform rash.

Previous medical history.—Arrived U.K. from India November 1949. 1943: Had malaria. No other relevant illnesses, apart from infective slow healing ulcers left shin.

Family history.—Father died twenty-two years ago—does not know cause of death. Mother and sister alive and well. Married July 1948; wife alive and well.

On examination.—Dusky erythematous maculopapular lesions, sharply circumscribed, affecting face, arms, buttocks and legs.

Scaly, marginated patch left leg over areas L.3, 4, and 5. Scars of old ulcers left shin.

All the skin lesions showed anæsthesia to pin-prick. The left foot showed weak dorsiflexion which has since progressed to complete foot drop.

Treatment and progress.—On September 14, 1951, treatment with diaminodiphenylsulphone (Avlosulfon) commenced with 50 mg. twice weekly, the dose gradually being increased until maintenance dose of 300 mg. twice weekly was reached—this is the dose he is receiving at present.

During this period the lesions have partially faded and have become flatter. There is no lessening in the degree of anæsthesia or the foot drop.

III. Male, aged 20, *West Indian.* (*Dr. John Franklin's case.*)

This case illustrated a major lepride, which histologically had some atypical features (Fig. 3).

History.—June 1951 noticed the skin of right leg, which had always been dry, was starting to crack and flake off.

Late August 1951 visited local doctor as it was spreading.

Late September 1951 noticed for the first time some patches of paler discoloration on the legs, and also a swollen second left toe.

For past three weeks noticed pains in both legs, right more than left; sometimes momentary, sharp and stabbing in character on outer side of right leg. Both ankles also painful, and the left one tender and swollen. He often feels as if something is continually squeezing the upper third of his right fibular region. No numbness felt, but often tingling in the whole of the right leg. He thinks that the muscles of thighs and legs are getting thinner, but has not observed any definite weakness.

November 1951, he sat near the fire, but did not seem to feel the heat as usual on his right leg.

He is well otherwise in himself.

Past history.—Epistaxis on and off since childhood, the last occasion being this December, but no nasal discharge. Clots of blood come away on clearing his nose in the mornings.

Family history.—Mother, father, one brother and two sisters all well. One brother died aged 14 months, cause unknown. Paternal grandmother also suffered with epistaxis. Family residence in Trinidad. Born at Mayaro where he lived for nine years. No history of contact as far as he remembers. From age 9 to 14 years in San Fernando. Family and brother-in-law, who lived with them, quite well. From age 14 to 20 years in San Juan. Has been in U.K. for past sixteen months for study.

On examination.—General condition fairly good, though rather on the thin side. Alert and co-operative.

Skin: Multiple lesions on legs, right more than left, and one on left upper arm. The lesions have a well-defined, reddish-brown, scaly, raised edge, with evidence of pale discoloration. All these areas show evidence of hypoæsthesia and hypoalgesia.

Nerves: Marked thickening of lateral popliteal nerves; slight thickening of ulnar nerves, which do not produce any sensory disturbance on pressure.

Motor: Definite evidence of marked weakness of dorsiflexion and plantar flexion of right foot, and inability to move left big toe, though ankle power is good.

Reflexes: Arm-jerks appear to be absent. Knee-jerks brisk, right more than left. Ankle-jerks: right sluggish, left present. Plantars flexor.

It was also noted that the left foot was warmer than the right, but the dorsalis pedis vessel was not palpable, probably owing to general thickening of tissues. Minimal œdema.

Left second toe showed considerable enlargement, being involved in a maculo-anæsthetic lesion.

The skin of both legs, apart from the well-defined lesions, appeared shiny, with scaliness.

Other systems.—Heart, lungs, abdomen—N.A.D. B.P. 120/70.

This case was subsequently operated on. Notes kindly provided by Mr. A. M. Burnford.

17.1.52: Operation—Performed by Mr. H. E. Harding. Anæsthetist: Dr. J. B. Wyman.

Left leg: Incision down centre of popliteal space inclined downwards and outwards towards the neck of the fibula.

Greatly thickened, white, œdematous nerve sheath encountered over peroneal nerve. This was followed up to a point just below the confluence of the sural branch at which point the nerve suddenly assumed its normal proportions again. Following downwards the nerve was found to be involved to a point about 2 in. above the neck of the fibula.

The whole of the thickened nerve sheath was easily excised and the nerve decompressed. At one point was an early nerve abscess.

Muscle about this area all looked healthy.

Right leg: A similar incision, but longer, was made to expose the affected peroneal and lateral popliteal nerves.

The peroneal nerve was grossly involved almost to the neck of the fibula and there were several abscesses present which must have seriously disrupted the continuity of the actual nerve fibres.

The peroneus muscle was pale, flabby and necrotic where the nerve entered it.

The lateral popliteal nerve was involved in the inflammatory process as far as its junction with the medial popliteal nerve. In this also there was abscess formation. In these nerves it was not so easy to strip off the nerve sheath, but decompression was effected.

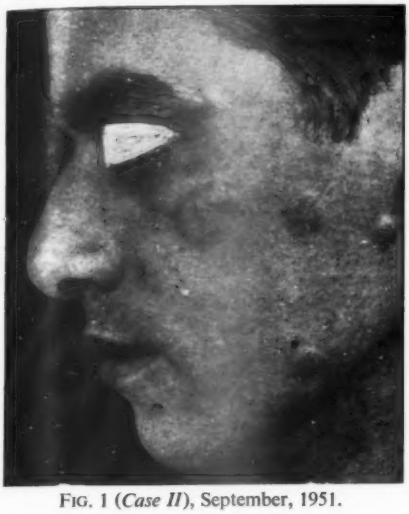

FIG. 1 (*Case II*), September, 1951.

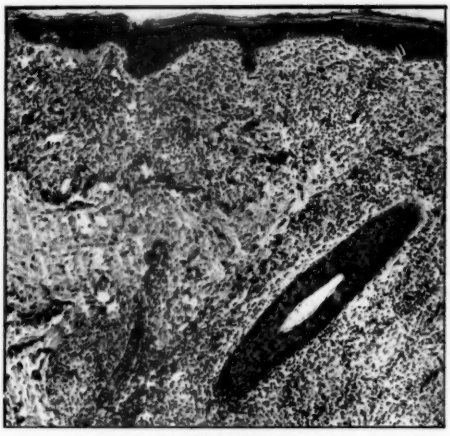

FIG. 2.

FIG. 2 (*Case II*). — Note granulomatous infiltration underneath the epidermis, with round cells and epithelioid cells. The granulomatous infiltration tends to extend up to the epidermis without any definite sub-epidermal zone, indicating typical tuberculoid histology. × 63.

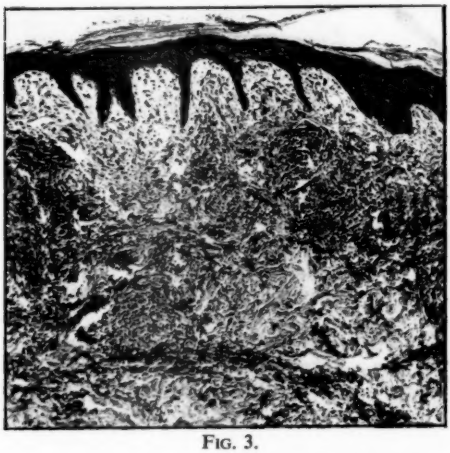

FIG. 3.

FIG. 3 (*Case III*). — The photomicrograph shows characteristic granulomatous infiltration with round cells and epithelioid cells. It is interesting to note, however, that, unlike Fig. 2, intense granulomatous infiltration stops short of the epidermis, leaving a narrow layer showing only a few infiltrated cells. This would indicate the lesion probably belongs to the atypical group of cases known as intermediate, or borderline cases, or atypical lepride. × 68.

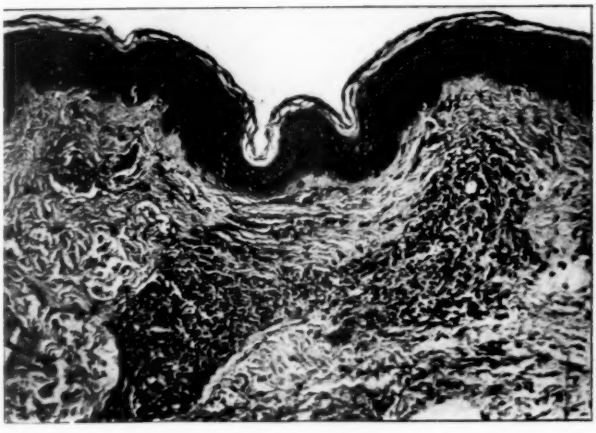

FIG. 4 (*Case IV*).—The photomicrograph shows characteristic appearance with the granulomatous infiltration stopping short of the epidermis. The infiltration in the dermis shows numerous macrophages, many of which show foam-cell degeneration; numerous acid-fast bacilli. × 116.

An interesting point with reference to this case is the intense infiltration of the peroneal nerve on the left, and the peroneal and lateral popliteal nerves on the right, both of which showed abscess formations.

IV. Female, aged 25. (*Sir George McRobert's case.*)

A characteristic, moderately advanced case of lepromatous leprosy, with a slight thickening of the ear, puffiness of the face, and some deformity of the nose. Lesions are seen throughout the body and there are some subcutaneous nodules in the arms and thighs.

The patient gives a history of only one year's duration, but this cannot be correct. Examination of the nose and skin shows many bacilli. Biopsy showed characteristic changes of lepromatous leprosy (Fig. 4).

Mr. George Qvist's case: Relapsed lepromatous leprosy with marked nerve involvement.

In addition to the above cases X-rays were shown of a patient of Mr. George Qvist's, who was in the Royal Free Hospital for the treatment of trophic ulcers of the feet (Fig. 5).

While there is considerable deformity of the right foot the X-ray picture shows more gross bony changes than one would anticipate. There is considerable rarefaction of the phalanges, absorption and necrosis of the metatarsal bones (Figs. 6 and 7).

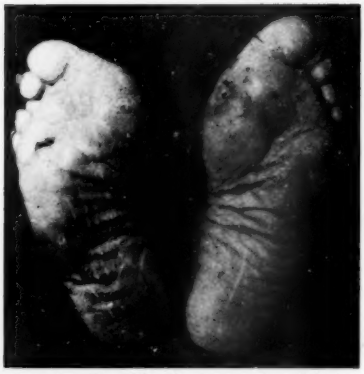

FIG. 5.—Trophic ulcers on soles of feet.

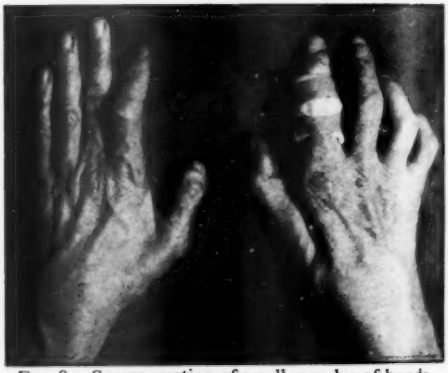

FIG. 8.—Severe wasting of small muscles of hands.

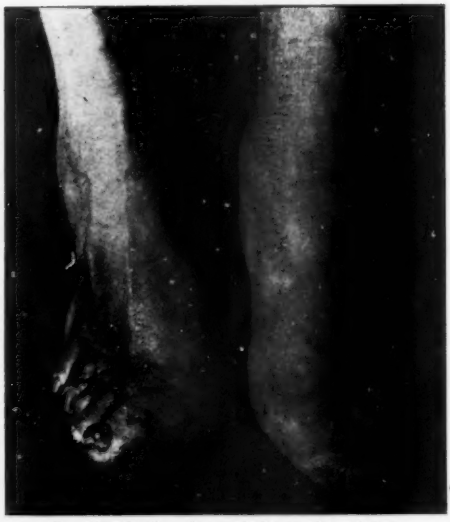

FIG. 6.—Deformity and shortening of feet.

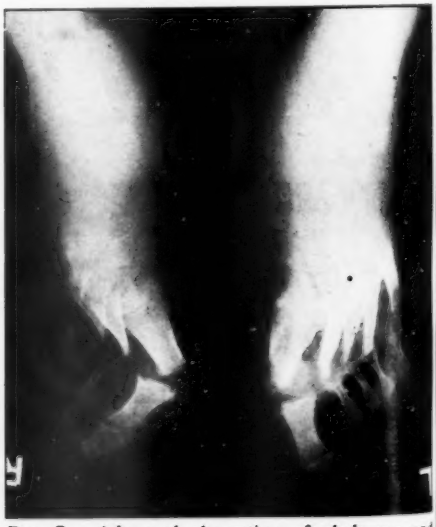

FIG. 7.—Advanced absorption of phalanges and metatarsals.

Such a case, so far as possible, is treated symptomatically. The patient who has deformity of the hands would find it difficult to use crutches (Fig. 8). Conservative treatment, therefore, should be undertaken, and if any operation was performed every effort should be made to retain a weight-bearing stump.

Dr. R. G. Cochrane, in reply to discussion, stated that he was interested that surprise was expressed that one handled cases of leprosy so freely, and emphasized that the generally accepted view was correct, that leprosy was a very mildly pathogenic disease, and that the healthy adult was relatively non-susceptible.

He mentioned, in passing, that the traditional view of leprosy arose from a mis-translation of a Hebrew word. In the early history of the Jewish people they were commanded to separate all persons who had diseases which produce permanent blemishes, and all such persons had to be put "without the camp". This group consisted of such conditions as psoriasis, leucoderma, chronic fungus infection, scabies, and possibly mutilations, and all these diseases were given one name—Zaraath. Unfortunately, when the Bible translators came to deal with this word "Zaraath", instead of translating it "a blemished man" they translated the word "leprosy". Hence the tradition arose that leprosy was a highly infectious disease.

In replying to a question from Sir George McRobert with reference to the boy attending school, Dr. Cochrane stated that when the condition was active and the lesions were erythematous and desquamatory, it was inadvisable for the boy to attend school. The lesions were now quiescent and largely resolving, and, therefore, he did not consider that the patient was in any way infective, and saw no reason why he should not attend school.

Two Cases of Felty's Syndrome with Features of Sjögren's Syndrome.—K. GURLING, M.D. (for R. S. BRUCE PEARSON, D.M.).

The association of chronic leucopenia with splenomegaly and rheumatoid arthritis is relatively uncommon and often known as Felty's syndrome. When kerato-conjunctivitis sicca and xerostomia occur in association with rheumatoid arthritis the description of Sjögren's syndrome is applicable. These 2 cases show features of both diseases and suggest that there is, in fact, a common pathological factor.

Case I.—Mrs. L. C., aged 71.

She first noticed rheumatoid arthritis when 18 years old and now has severe deformities of the hands, wrists, elbows, hips and knees indicating inactive disease. In 1947 she noticed dryness of the mouth and severe irritation in both eyes. Filamentary keratitis was present and corneal ulcers developed; she is now almost completely blind due to corneal opacities. One year later she had bilateral parotid swellings and a leucopenia was discovered which still persists.

Past history.—Nil relevant.

Family history.—None of arthritis.

On examination.—Bilateral corneal opacities with ropy mucus on the conjunctiva. Pale, dry skin. Mouth dry with coated tongue. Respiratory system: Emphysema with unproductive cough. Central venous system: Moderate arteriosclerosis. B.P. 170/105. Abdomen: Spleen readily palpable; liver not enlarged.

Investigations.—W.B.C. 1,750. Neutros. 45%, lymphos. 40%, monos. 5%; Hb 78%; R.B.C. 4,200,000; colour index 0·93. B.S.R. 27 mm. (Wintrobe corrected).

Sternal marrow biopsy shows some hypoplasia of the white cells series.

Schirmer's test—Right eye 2 mm.; left eye 2 mm.

Salivation—Volume in 20 minutes, 2·0 ml. After 1/6 grain pilocarpine, 6·0 ml.

Case II.—Mrs. K. L., aged 58.

In 1946 she developed widespread rheumatoid arthritis and shortly afterwards a leucopenia was noticed; the spleen was not palpable. Treatment with liver made no difference to the white count, but after 1948 the arthritis began to improve and is now quiescent. In September 1951 the spleen was found to be enlarged and at this time she noticed a dry, sore mouth.

Past history.—Pleurisy 1936.

Family history.—None of arthritis.

On examination.—Pale woman with fine skin; not pigmented. Tongue smooth, red, fissured and dry. Typical deformities of the hands, shoulders, &c., indicating chronic rheumatoid arthritis. Respiratory system normal. Central venous system normal. B.P. 140/90. Abdomen: Spleen enlarged and freely palpable; liver also enlarged. Eyes: A little ropy mucus on the conjunctiva. Under the slit lamp there is evidence of filamentary keratitis with typical staining with 1% rose bengal. (Mr. R. P. Crick.)

Investigations.—W.B.C. 1,900. Neutros. 12%, eosinos. 2%, lymphos. 79%, monos. 7%; Hb 92% (9·2 grammes); R.B.C. 3,600,000. M.C.V. 82 c.μ. Platelets 95,000.

Sternal marrow biopsy shows no evidence of leukæmia or obvious upset of the white cell series.

Schirmer's test—Right eye 7 mm.; left eye 12 mm.

Salivation—Volume in twenty minutes, 1·5 ml. After pilocarpine 1/6 grain, 22·4 ml.

Parotid gland biopsy shows evidence of atrophy of the parenchyma with some round-cell infiltration.

Case II was treated with ACTH in doses of up to 100 mg. daily with improvement in the arthritis. The white count rose but was never above 3,000 per c.mm. and there was no change in the size of the liver or the spleen.

The eye irritation was relieved though lacrimation was not increased and no change was noticed in the mouth. Splenectomy will be carried out by Mr. Harold Edwards in the near future.

Two Cases of the Thibierge-Weissenbach Syndrome.—G. A. COOMBS, M.B., Luton and Dunstable Hospital, Luton (for T. PARKINSON, M.D.).

Case I.—Mrs. E. M. D., aged 49, has suffered from Raynaud's syndrome since 1933. Bilateral cervical sympathectomy, in 1935, failed to relieve her symptoms. In 1940, she noticed progressive dysphagia, and in 1948 she became constipated. Since then she has lost weight considerably.

On examination.—On admission to hospital in October 1950 she was wasted. There was gross scarring of the finger tips and several hard subcutaneous nodules on the hand. There was no generalized scleroderma, nor were there any telangiectases.

Investigations.—Barium swallow: "Rat-tail" narrowing of the lower œsophagus. No hiatus hernia. Barium enema: Grossly dilated colon. X-ray of hands: Subcutaneous calcinosis. Hæmoglobin: 68% (Haldane).

Subsequent progress.—On a bland diet and alkalis she lost her dysphagia and gained 2 stones in weight. In April 1951 she was readmitted complaining of lassitude, and while she was in hospital she had a hæmatemesis. On admission her hæmoglobin was 40% (Haldane), R.B.C. 2,500,000 per c.mm. With intravenous iron and a blood transfusion she improved and is now very well with a hæmoglobin of 92% (Haldane). There is now no dysphagia although she is taking a modified gastric diet, and a recent barium swallow shows very little delay at the lower œsophagus.

Case II.—Mrs. M. F. S., aged 42, developed Raynaud's syndrome in 1944. Bilateral cervical sympathectomy was performed in 1950, but no improvement followed.

Examination.—Two telangiectases on the cheek and forehead. Several telangiectases on the lips have appeared within the last six months. The skin of the hands is dry and thickened and there is scarring of the finger tips. There are several telangiectases on the left hand.

Investigations.—Barium swallow: No obstruction to passage of barium. X-ray of hands: No calcinosis.

Comment.—Both these patients show features of the syndrome, sometimes called the Thibierge-Weissenbach syndrome, in which scleroderma or sclerodactyly, Raynaud's phenomenon, calcinosis cutis, telangiectases and visceral lesions occur in various combinations. The use of an eponymous title for this disorder has the advantage of emphasizing the variable manifestions. Neither patient had relief from sympathectomy. Hunt, J. H. (1936, *Quart. J. Med.*, **5**, 393), has suggested that sympathectomy often helps in this disease; but as these cases show, there is very often no improvement after operation. Indeed, the history of Raynaud's phenomenon persisting after sympathectomy is often the earliest symptom of the syndrome. It is important, therefore, in all patients with Raynaud's syndrome to look for other features of the Thibierge-Weissenbach syndrome before considering operation. A photograph of the second patient taken at the time of operation shows that the two telangiectases were present at that time, and perhaps the operation would not have been done if their significance had been recognized.

The fact that the first case responded so well to a bland diet by losing her dysphagia suggests that a great deal of the discomfort suffered by these patients is due to a chronic œsophagitis and is not solely a mechanical effect. Her hæmatemesis also bears this out, suggesting that there was active ulceration taking place. In this respect the symptoms, signs and pathology bear a close resemblance to hiatus hernia, and as Bourne, W. A. (1949, *Lancet* (i), 392), has pointed out, the two conditions are sometimes associated.

Section of Laryngology

President—F. C. W. Capps, F.R.C.S.

[*February* 1, 1952]

DISCUSSION ON OPERATIVE REMOVAL AND PLASTIC REPAIR IN CASES OF CARCINOMA OF THE HYPOPHARYNX AND UPPER ŒSOPHAGUS

[*Abridged*]

Mr. R. D. Owen: In assessing the operability of lower pharyngeal and upper cervical carcinomatous growths, we must determine certain essential details:

(1) The degree of dysphagia. It is important to know whether the whole lumen is involved or not.

(2) The degree of mobility of the vocal cords.

(3) The upward and downward extent of the growth.

(4) Has the infiltration spread beyond the muscular wall to outside structures in the neck?

(5) It is wise to palpate the thyroid gland and to ascertain the mobility of the larynx when moved against the prevertebral fascia.

(6) Finally, the neck must be examined for secondary lymph nodes.

We find out these details by direct and indirect laryngoscopy and endoscopy and also by soft tissue X-rays and tomographs, but there are occasions when we have to make a direct approach through the neck before we can be certain of the downward spread of a cervical growth.

Accurate diagnosis of localization is absolutely necessary to properly planned treatment, because we have to bear in mind two essential factors: to try and eradicate the disease, and to maintain or restore function.

Epithelioma of the hypopharynx has five starting points, from above downwards, in the following order: (1) Aryepiglottic fold; (2) pyriform fossa; (3) lateral pharyngeal wall; (4) posterior pharyngeal wall; (5) postcricoid area; and we must also consider the cervical œsophagus. Although these areas are quite close to one another they differ in symptoms, in prognosis and in details of treatment.

There are two ways in which we can attempt to deal with these lesions surgically. We can approach and excise the tumour by performing a lateral transthyroid pharyngotomy, which means saving the glottis, or we can be more radical and carry out a pharyngo-laryngectomy. The latter invariably means a plastic repair in order to restore function.

An early aryepiglottic fold lesion—and I emphasize "*early*"—can be excised without interfering with the glottis, and the pharynx can be closed by primary closure. Similarly, an early and localized growth of the lateral pharyngeal wall can be dealt with by local excision and sometimes primary closure, but growths of the pyriform fossa and postcricoid region are in a different category. These areas are of evil repute, and so is the cervical œsophagus.

The question arises whether we are prepared to compromise with cancer to try and save the larynx, especially when an early growth arises from the pyriform fossa or the postcricoid area. With an early lesion, and with mobile vocal cords, we may find ourselves tempted to peel off a pyriform fossa lesion from the side of the larynx, or an early postcricoid growth from the postcricoid plate, and to follow this later by radiation, or the other way about.

I must confess that as I get older I pay less respect to the glottis, because experience has taught me that preserving the larynx has not improved my cure rate.

In some schools the general principle in operative technique is to respect the glottis when there is no involvement. The mobility of the cords therefore becomes of the utmost prognostic importance, but it is vital to remember that mobile vocal cords are no guarantee that the larynx is not involved, even with an early postcricoid growth and upper cervical carcinoma. When, therefore, does one decide to perform the lateral transthyroid operation as against a pharyngo-laryngectomy, in hypopharyngeal lesions?

I suggest that the indications for a lateral transthyroid pharyngotomy are:

(1) A localized aryepiglottic fold carcinoma.

(2) A limited growth involving the lateral pharyngeal wall, starting somewhere near the level of the apex of the arytenoid but well away from the laryngeal opening. This can be removed without interference with the larynx, and, what is just as important, the pharyngeal wall can be sutured completely. It is amazing sometimes to find how a fungating mass, even overhanging the arytenoids and vocal cords, can have a very limited pedunculated base on the lateral wall, and be easily removed, followed by a primary closure.

(3) A posterior pharyngeal wall lesion with or without extension to the lateral walls. The technical interest attached to this type of lesion is the fact that any excision of a segment of the posterior pharyngeal wall calls for an immediate plastic repair by a skin flap.

(4) An early lesion of the cervical œsophagus where the spread does not come up beyond the cricopharyngeus and where there is complete mobility of the vocal cords, and of course where the œsophagus can easily be separated from the posterior wall of the trachea and the back of the larynx.

All the other lesions such as a pyriform fossa carcinoma, postcricoid carcinoma with or without

downward extension to the cervical œsophagus, or a primary carcinoma of the cervical œsophagus which is infiltrating into the wall of the trachea—these can only be dealt with by a pharyngo-laryngectomy.

It may be that some are of the opinion that transthyroid pharyngotomy as an operation should not be used for any hypopharyngeal growth, but I cannot agree with this where the lesion is a very early one and to this extent I still follow Trotter's teaching.

Briefly let us consider the early and more advanced lesions of the pyriform fossa, postcricoid area and the cervical œsophagus.

Early pyriform fossa carcinoma.—Once *early* pyriform fossa carcinoma has been diagnosed by direct examination, and confirmed by biopsy, the proper treatment is surgical removal (Fig. 1). It is important, however, to make quite clear what is meant by surgical removal. It means a block dissection of the neck on the same side as the lesion, the removal of the corresponding thyroid lobe, the hyoid, the larynx, and the involved segment of the pharynx on the same side. This enables one to retain a wide strip of the posterior pharyngeal wall in continuity with the œsophagus (Fig. 2). It is important to take great care to dissect out the healthy pyriform fossa, and when this is done one can assess more clearly the necessary free margin of safety. In my opinion the operation is carried out with greater ease when the removal is performed from above downwards, and the larynx need not be detached from the trachea until the pharynx has been closed completely.

(J. M. Williams)

FIG. 1.—Early pyriform fossa carcinoma shown in Fig. 2.

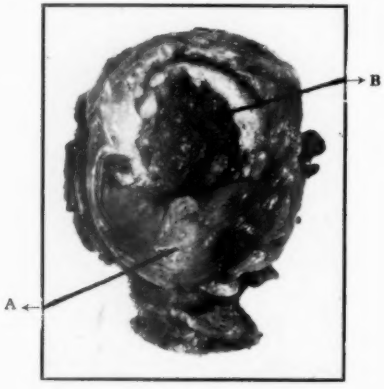

FIG. 4.

A.—Postcricoid surface reflected back to show absence of growth.

B.—Segment of cervical œsophagus and laryngo-pharynx removed—showing localized epitheliomatous growth of posterior wall.

The kind of skin flap to be used is a matter of choice. I prefer the U-shaped flap, because of the ease with which the closed pharynx in the mid-line can be sutured to the undersurface of the skin flap in the final closure of the wound. This step gives an added security against leakage during the healing stage. In addition, the U-shaped flap gives an excellent exposure for a block dissection when an oblique incision is made outwards towards the mid-line of the clavicle.

I have mentioned previously that cancer of the pyriform fossa is of evil repute, and it is my opinion that in the absence of any clinical evidence of cervical metastasis, it is always wise, even with an early primary, to commence treatment by carrying out a block dissection. The procedure can be regarded as a one-stage operation combining excision of the primary and the secondary lymph nodes.

In every operable case it is wise to carry out the combined operation as a one-stage procedure, and never attempt to preserve the larynx, no matter how early the involvement. Where the pyriform fossa lesion has spread to involve the posterior pharyngeal wall and the posterior aspect of the larynx, it is then impossible to make use of the posterior wall mucosal strip for the purpose of repair. Nothing less than a pharyngo-laryngectomy with the removal of a complete segment of the pharynx should be performed.

Postcricoid carcinoma.—The incidence of this disease is far more frequent in females than in males. It is not usual for one to be fortunate enough to be able to diagnose the disease in its early stages. As a rule the growth is seen creeping up to the level of the arytenoids, with or without fixation of the vocal cords. It frequently spreads laterally to involve the whole lumen, and, more often than not, spreads downwards towards the cervical œsophagus.

In these cases surgical removal is possible only by performing a pharyngo-laryngectomy.

During the last twenty-five years this operation has been performed by many surgeons, and as a rule in two stages or even in three, where a bilateral block dissection of secondary lymph nodes had to be the first step.

FIG. 2.—Resection of growth (Fig. 1) leaving behind posterior pharyngeal wall for reconstruction. Larynx seen separated from upper cervical œsophagus. Catheter seen to show the œsophagus.

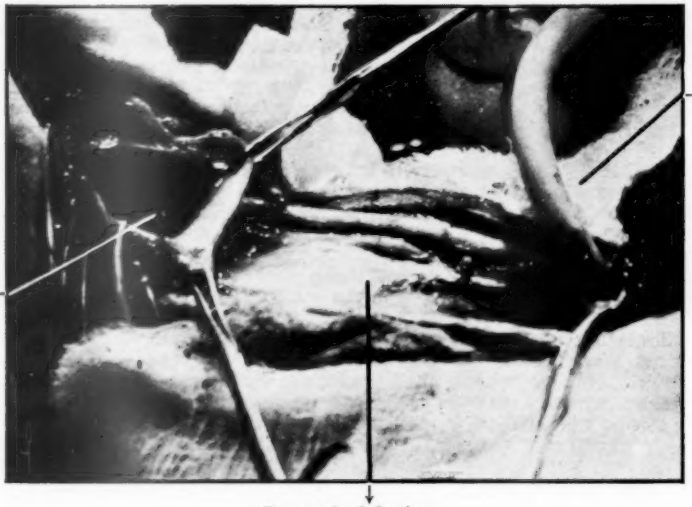

FIG. 3.—The problem of reconstruction.

In operable cases the excision of the growth is not a difficult procedure. The real problem is the restoration of function. Fig. 3 shows what remains in the neck after a whole segment of the pharynx, larynx and a portion of the upper œsophagus have been removed.

The repair of this defect is not a simple matter, and it is here that the laryngologist seeks the help of the plastic surgeon if a primary closure is to be carried out. In 1949 I described how Mr. Emlyn Lewis and I had for about two years been attempting primary closure with skin grafting, as compared with a secondary closure of the pharyngostome. Mr. Lewis will describe the technique.

An attempt to save the larynx, even with a very early postcricoid growth, should never be made. The larynx must be sacrificed.

Localized carcinoma of the upper œsophagus and laryngo-pharynx.—The type of operation to be performed for a carcinomatous lesion in the upper œsophagus or the *posterior* wall of the laryngo-pharynx depends entirely on the degree of involvement. There is a school of thought which says that under no circumstances ought one to attempt to save the larynx, but in my opinion one should not be so dogmatic.

There are *early* cases to be seen where the growth is localized to the posterior wall of the laryngo-pharynx, with a limited spread to the upper œsophagus (*see* Fig. 4). In these cases a complete segment of the lower pharynx can be removed by performing a lateral pharyngotomy on the left side without exposing the area of the growth during the operation. It is a straightforward procedure to separate the pharyngeal tube from the back of the cricoid, and the opposite recurrent laryngeal nerve need not be traumatized. The defect can be repaired by making a gutter with a good lateral skin flap as originally planned by Trotter over thirty years ago and more recently modified by Wookey.

The same applies to a localized growth of the cervical œsophagus. The lateral transthyroid pharyngotomy approach can be made use of when the growth arises from the posterior wall and with a limited lateral spread.

The modified lateral flap, as suggested by Wookey, is reliable, provided that the blood supply to the upper portion of the sternomastoid can be left undisturbed. Where extensive dissection for secondary lymph nodes has to be carried out at the same time with the removal of the sternomastoid, the peripheral blood supply to the skin flap may be jeopardized. This means that extreme care must be exercised that no undue tension exists in any of the areas where cutaneous mucosal approximation is carried out. This particularly applies to the suturing of the distal end of the œsophagus and the skin margins.

In stressing the steps in technique that make the difference between success and failure, I would draw attention to two other important points in the operation of transthyroid pharyngotomy in *early* cases.

First of all, there is the importance of avoiding a double abductor fixation of the cords when a segment of the laryngo-pharynx is removed. This can be brought about in two ways. When the approach is made from the left side, which is the usual way, the left recurrent has got to be sacrificed. The right can also be damaged due to excessive rotation of the larynx when dissecting the pharynx from the posterior surface. Also both cords can become fixed as the result of the immobility produced by the skin flap being sutured too close to the level of the arytenoids, and the subsequent scarring and fixation of the posterior aspect of the larynx and skin to the prevertebral fascia. This means that the new upper pharyngeal stoma, when the gutter has been closed, is situated at the glottic level, so that when fluids are swallowed there is a spill over into the open glottis and trachea, resulting in coughing and spluttering. This makes life a misery, and the only relief is a laryngectomy.

The second point is that as a result of the fixation of the cords a tracheotomy becomes a permanent feature, and if the opening into the trachea is too close to the lower œsophageal stoma, with a poor bridge of skin in between, then the problem of closure for the plastic surgeon is a very formidable one indeed.

To summarize, it is absolutely necessary to have a clear picture of the extent of the growth, for properly planned treatment.

The presence of mobile vocal cords, with localized posterior wall carcinoma of the laryngo-pharynx often means that a whole segment of the lower pharynx and upper œsophagus can be removed without sacrificing the larynx.

Postcricoid carcinoma or pyriform fossa carcinoma, however early, means removal of the larynx to ensure some measure of success. A strip of the posterior pharyngeal wall left behind facilitates primary closure.

Block dissection on the same side as the pyriform fossa lesion is always carried out whether nodes are palpable or not. Where there is an annular involvement of the whole of the pharyngeal or œsophageal lumen below or above the glottic level, a complete segment must be removed as well as the larynx (pharyngo-laryngectomy) and if the nodes are palpable it is better to do a bilateral block dissection first.

For primary closure I prefer the U-shaped flap to the T and Z flaps, but this is a purely personal choice.

Mr. Emlyn Lewis: Trotter in his Hunterian Lecture on hypopharyngeal growths in 1913, when describing his operation of lateral pharyngotomy, emphasized certain technical details concerning the use of the flap to be used for covering either the prevertebral fascia or the posterior surface of the larynx. Those technical details apply today. I would add one other, namely that the best dressing for a raw surface is a skin graft.

In cases in which the larynx has been removed it behoves the surgeon to reconstruct the gullet as quickly as possible, by as few operations as are consistent with sure repair. This is obvious for the comfort of the patient and also necessary for the achievement of œsophageal speech. If the repair is delayed, patients acquire a whispering speech. This habit developed, the production of successful œsophageal speech is much impaired. Excision and repair should be carried out in one operation if possible, and for the last three years in suitable cases we have attempted this by means of skin grafting, while in other selected cases Mr. Owen has been able to do it without resorting to a graft.

When skin grafting is used the new gullet is made by wrapping a skin graft, raw surface outwards, around a hollow former, or in the case of a stent former, a tube is fixed in the stent. The hollow tube acts as a saliva drain. The former mostly used is made of portex, and with some modifications shaped like a Gluck's tube. The expanded upper end is fixed in the pharynx by a purse-string suture, while the lower end lies snugly in the lumen of the œsophagus. The skin flap is sutured over the former, and to ensure accurate apposition between the graft and the undersurface of the flap, wool, wrung out

of paraffin and flavine, is carefully packed over the surface of the neck and held in position by Lastonet. The head and neck are immobilized by either plaster of Paris or large bulky dressings, and by sand-bagging. The former is removed on the fourteenth day, and replaced by a similar one. This must be held for ten to thirteen weeks in order to counteract the contractile phase of the graft. Following the ten to twelve week period we have performed intermittent dilatation to prevent stricture at the graft œsophageal junction.

Comments on flaps used and bearing on repair.—The standard flaps used for pharyngo-laryngectomy are unsound, the majority depending on a lateral base. Owing to the laterally based flap being limited in its width, it may not be possible to suture its lower margin to the cut end of the œsophagus without tension when the œsophagus has had to be divided low down behind the manubrium. The safe length of such a flap may not be adequate to meet the full requirements of a Wookey type of repair, even if the raw surface on the right side of the neck is grafted. This type of flap causes vertical shortening of the neck.

Apart from the above objections the T-shaped flap produces a vertical scar in the mid-line on the prevertebral fascia. Such a scar may interfere with the blood supply of any flap subsequently used to produce lining for the repair. Neither of these flaps provides a good bridge of skin between the cut ends of the œsophagus and trachea, which is essential if secondary repair is to be 100% certain. Fibrous tissue bridging the œsophago-tracheal junction is poor stuff upon which to rely for successful repair.

The U-shaped flap.—My preference is for this flap, whether repair is to be primary or secondary. It is based above at the mastoid processes and can be made as long as desired, the curve of the U being brought down over the front of the chest wall if necessary. It is safe and can be split to encircle the tracheostomy. Its advantage in primary repair is that the skin suture line is far removed from the graft area and, in secondary repair, flaps for lining can be made within its confines thereby avoiding crossing scars when making them.

Providing the length of the flap is adequate, as it should be, one is assured of a healthy bridge of skin between the cut ends of the œsophagus and trachea, whether the œsophagus has been cut above or below the level of the trachea.

Wookey repair.—If this is to be successful, the flap must be long enough to make the necessary folds, which in transverse section should assume a shortened, broad letter "S" with the top end of the "S" being continuous with the skin of the left side of the neck and the lower end of the "S" passing on to the raw surface of the right side of the neck. There must be a raw surface on the right side of the neck which should be grafted. The S-shape can only be assured by careful meticulous suturing not only of skin to mucosa but also by transfixing sutures fixing it to the prevertebral fascia, especially over to the right side of this fascia. The free end of the flap should be sutured down the right side of the middle line of the neck, and free of tension. A raw surface on the right side of the neck must result; it should be skin grafted. The "S" shape is maintained by placing a suitably sized tube in the pharyngeal gutter and gently strapping the lower part of the "S" over the tube on to the left side of the neck. If these precautions are taken, secondary closure is simple providing care is taken to offset the lining suture line from the cover suture line.

In failed Wookey, and for repair of the median pharyngostome, I prefer to use an inturned lining flap based on the left margin of the opening (Figs. 1 and 2). The flap is carefully sutured over a tube to an incision which surrounds the remaining margins of the opening. One always attempts to bury this suture line so that the tissues in sealing themselves reinforce the suture line. The raw surface on the left side of the neck from which the flap came, and also the superficial raw surface of the lining flap, are covered by a thin split skin graft. The neck is splinted either by bulky dressings or sandbags.

FIG. 1.—Inadequate pharyngeal gutter. Referred to as a "failed" Wookey.

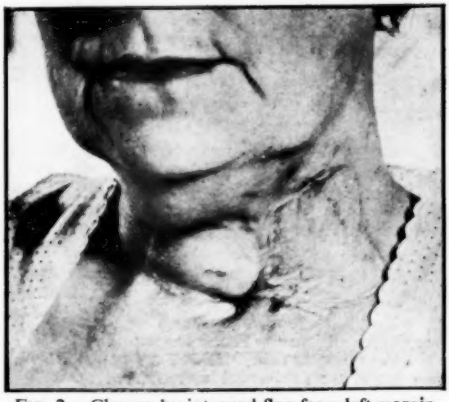

FIG. 2.—Closure by inturned flap from left margin of gutter. Skin graft to the raw surface.

The dressing is taken down about seven to ten days later, and the tube which has acted as a former is removed (Figs. 3 and 4).

At first, only liquids are permitted by mouth. About two to three weeks later, full diet should be possible, and training in œsophageal speech proceeding. *Removal of the hyoid bone* at the primary operation is advocated. This produces some antero-posterior collapse of the pharyngostome, and reduces movement at the suture line when secondary repair is performed. *Gastrostomy* is advocated as beside other advantages it permits a rigid restriction in oral feeding during the healing of the repair. *Primary X-ray therapy* for those cases which have operable growths we believe to be contra-indicated. Mr. Robert Owen on his part has very decided views, and I have encountered such cases where post-radiational œdema has delayed second stage repair. In other instances, closure has been complicated by post-radiation necrosis, and multiple operations have been necessary to achieve closure. We have under our care at the present moment, a case in which Mr. Owen carried out pharyngo-laryngectomy with primary repair. The repair proved successful but later necrosis of the skin flap developed, and now the skin of the neck over an area of 9 square inches is breaking down, and a fistula has formed. A chest pedicle has been made for repair.

The presence of hair in the reconstructed lumen has been encountered. We believe the best thing is to remove the hair as and when it causes trouble. Radiation depilation is not successful, as we have

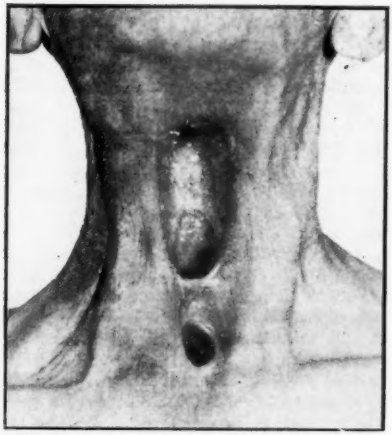

FIG. 3.—Median pharyngostome. Note bridge of healthy skin between trachea and œsophagus.

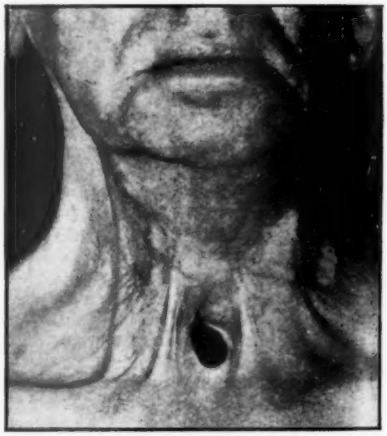

FIG. 4.—Pharyngostome closed by inturned flap from left side of opening. Skin graft to the surface.

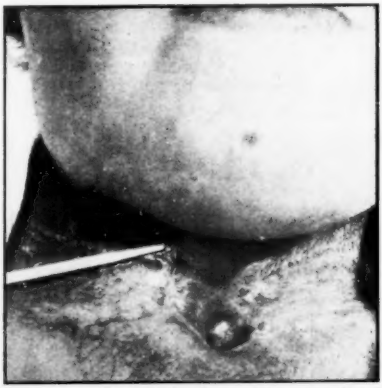

FIG. 5.—Condition following primary repair using skin graft around former. Probe points to a break-down using a lateral flap. Healed subsequently. Note contracture in vertical direction of neck, and chin pulled down.

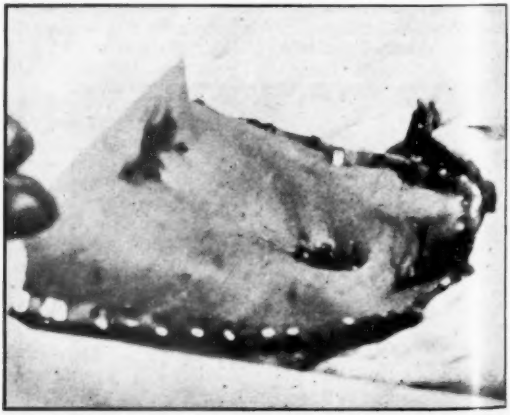

FIG. 6.—Median pharyngostome. Large U-shaped flap. Note bridge of skin between œsophagus and trachea. Flap split to encircle tracheostomy.

encountered the trouble in cases which had been previously irradiated therapeutically. I have replaced the skin of the neck by a hairless skin graft from the inner side of the arm, as a preliminary operation, then later used this skin for the inturned lining flaps. The procedure is tedious, and even so hair has grown.

In conclusion, we believe primary repair with skin graft has a place, and should be developed in suitable cases. There can be no doubt as to its desirability (Fig. 5).

We advocate early certain secondary closure in other cases. We believe this can best be achieved by using a U-shaped flap at the primary operation (Fig. 6). It provides that all-important bridge of skin between the œsophagus and trachea. In the average closure this can be done by means of an inturned lining flap covered by a thin skin graft. Technically I would emphasize certain points in successful repair.

(1) Oblique division of the œsophagus.
(2) If in doubt, any flap should be somewhat larger than that required.
(3) It should be handled with care, and as thick as the skin and subcutaneous tissues of the neck will permit and should include the platysma, and, if necessary, part of the sternomastoid. It should not be undermined any more than is adequate for the repair.
(4) The flap should never be sutured under tension.
(5) Suturing must be meticulous and of the vertical mattress variety, in order to evert the suture line, and skin to mucosa suture must be accurate if stricture is to be avoided.
(6) All sutures in the lining flap should have their knots on the inner surface of the lumen.
(7) Overlying suture lines should be avoided. Always offset them, and always evert.
(8) All raw areas should be grafted.
(9) It is wiser to leave a raw surface than to close it by producing tension; it can always be grafted.
(10) Fixation of the head and neck in the post-operative period is imperative. It is wiser to overdo this than to neglect any precaution.

Mr. Gavin Livingstone: The treatment of cancer of the upper end of the œsophagus by surgery has, in recent years, come into prominence, and I believe there are three main reasons for this, namely:

(1) The disappointing results of radiotherapy.
(2) The security given by the antibiotics.
(3) The co-operation of the plastic surgeon.

I have written to several of the larger radiotherapy centres in the country and asked for an opinion on the results, or figures for the last ten years, if they are available, of the treatment of postcricoid malignant disease. The answers I have received were almost all gloomy and pessimistic. It was generally conceded that of all cancer of the mouth and throat, the postcricoid gave the poorest results with radiotherapy, and it seems to me that X-rays with a 250 kV. unit have little or no place in the treatment of growths in this special region.

Radiotherapy centres which have super-voltage units may later achieve satisfactory results but these centres are few, as up and down the country the average plant has only 250 kV.

A further point against radiotherapy is that tissues which have been irradiated do not lend themselves to surgery, and although a laryngectomy may be undertaken after irradiation, a pharyngo-laryngectomy often results in disaster due to the flaps breaking down from impaired vitality.

The second reason which has made the pendulum swing towards drastic surgery is the general control of infection by the use of antibiotics. Nowadays when planning the extent of the operation the danger from sepsis does not enter into the picture. The discomfort to the patient of frequent dressings made necessary by a salivary fistula, has been minimized when compared with the pre-penicillin era, and when fistulas do occur they are nothing like the trouble they were in the olden days.

The third, and I think very important, reason for the preference for surgery, has been the co-operation and interest of the plastic surgeons in the reconstructive work entailed by these pharyngo-laryngectomies.

I have been fortunate to have been associated with the plastic units at Stoke Mandeville and at Oxford, under the direction of Professor Kilner and I am sure that the results achieved and the many pitfalls avoided, have been due to their close co-operation.

Because of these three reasons, I feel that surgery should be the method of choice in the present state of our knowledge in cases of carcinoma around the cricopharyngeal sphincter.

When making the choice of operation it is difficult to decide the size of the growth. There are often extensions in the submucous layer larger than the part which is ulcerated. The lower limit is especially difficult to assess, little help is obtained from œsophagoscopy or barium swallow, and often no instrument can be passed through the stricture, making examination below the growth impossible. A soft lateral X-ray frequently gives the most satisfactory picture.

Whatever the size, growths of the postcricoid region need bold and extensive surgery if the disease is to be removed in its entirety, and there is no place in the surgery of cancer in this area for any operation other than total removal of the larynx and the whole of the lumen of that portion of the œsophagus which is involved. Any modified operation, which leaves portions of lumen or preserves part of the larynx will reduce the likelihood of getting a complete cure. In the operation the mass removed should include the glands if they are involved, all muscles attached to the larynx, all of the hyoid bone and as much of the trachea as is necessary. The whole of the thyroid gland may have to come away and

should be removed if there is the slightest suspicion of involvement. I have had no trouble with the parathyroids, but when in doubt about their removal, the calcium metabolism should be checked post-operatively for a few days. It is important to make a separate opening for the tracheostome and leave as wide a bridge of skin as is feasible. In this way the plastic reconstruction is easier and the danger of a tracheo-œsophageal fistula is minimized. It is advisable to do a bronchoscopy at the end of the operation, and the blood which may have passed the anæsthetist's cuff tube should be aspirated.

Owen in his Presidential Address (1950, *Proc. R. Soc. Med.*, **43**, 157) states that he is in favour of doing a gastrostomy on most of his patients prior to operation. I prefer not to do this as a routine if it can be avoided, and if necessary feed the patient through a nasal tube. The stomach after a gastrostomy shrinks, and patients dislike being fed this way.

Choice of reconstruction.—If the operation is planned in two or more stages, there is little to choose between the different flap incisions. You all know the central incision with equal flaps and the Wookey type with the long rectangular flap which when folded round on itself is used to reform the upper part of the gullet. I am now showing a slide of these and various other incisions, each of which has its advocates. I prefer and will in future use the Z-shaped one.

The reconstruction of the gullet may also be done at the primary operation by means of a Thiersch skin graft wrapped around a large polythene or portex tube. This method was used by Mr. Negus and I have been using his type of tube with minor modifications. Ideally, I think the tube should be oval or D-shaped about 1¼ in. by 1 in. in diameter and funnel-shaped at the top. In this way the dead space at the sides is reduced and the chances of the graft not taking are minimized.

This type of reconstruction offers the following advantages:

(1) Whatever length of œsophagus is removed a graft can always be cut to bridge the gap and join the ends.

(2) Only one operation should be required. This is important when advising and persuading the patient to have surgery as opposed to radiation therapy.

(3) The time in hospital is reduced when compared with the two- or three-stage methods of closure, and, with the shortage of beds, this is an advantage.

The difficulties which may occur with this skin graft reconstruction are usually due to errors in technique and should in time be solved.

There is, for example, a tendency to stenosis at both upper and lower ends of the graft and for this reason I now leave the polythene tube in situ for under three weeks and not for six months as has been advocated.

In one of the cases shown to-day there was almost a tragedy; about six hours after the stay sutures were cut at the first dressing the polythene tube slipped down and caused obstruction to respiration, until it was removed as an emergency. Following or perhaps due to this incident, a fistula developed into the tracheostome and had to be closed by a small skin flap. I think the formation of a fistula is a real danger and the tube should extend well down into the œsophagus; also at the lower end the wall should be thinned to make it more pliable and soft, so that no fraying or rubbing will occur with head or body movements. Another complication is the difficulty to inspect, let alone dilate, the lower stricture as the tightness of the upper one does not allow instrumentation. But in this patient neither stricture is causing inconvenience and on barium swallow there is no gross hold-up, the patient continues to swallow easily.

The development of œsophageal speech is much more difficult after pharyngo-laryngectomy than after a simple laryngectomy; this is probably due to the removal of all the pharyngeal musculature although I doubt whether there is a functioning cricopharyngeal sphincter even after a simple laryngectomy. In spite of this, fairly adequate speech can be developed with training. Patients seem to prefer a pharyngeal as opposed to an œsophageal reservoir for air, but for longer phrases in one breath the œsophagus must be used.

I have had three cases referred to me recently and I was unable to operate on any of them.

In one the growth extended so low down in the gullet I did not think I could get the whole of it away and advised no treatment. This patient died in six weeks.

The second, a woman aged 43 with a Paterson-Brown Kelly syndrome, who was having a routine follow-up was found to have a very small ulcer in the postcricoid region. I was all keyed up to operate especially in view of this discussion, but nothing I could do would persuade her to have an operation which meant losing her voice. I have sent this case with regret for ray therapy.

The third was aged 85 with senile mental decay and I advised no treatment as she was still swallowing freely.

At the risk of being dogmatic I wish to summarize by emphasizing three points in the treatment of postcricoid cancer:

(1) While the results of radiotherapy are so disappointing radical surgery is the treatment of choice.

(2) The only operation undertaken should be a total pharyngo-laryngectomy.

(3) If possible the reconstruction of the gullet should take place at the primary operation.

Mr. **J. P. Reidy:** My experience is confined to cases of:

(1) Carcinoma of pyriform fossa. (2) Postcricoid carcinoma.

In these the operation of laryngectomy or total pharyngo-laryngectomy has been indicated.

There is a fruitful field of co-operation in this sphere of surgery, where the general surgeon or laryngologist has undertaken as wide an excision as desirable, and the plastic surgeon has completed the repair as planned between them. The operation is extensive, and it may be said that the results are as yet not permanently successful. On the other hand, there are no better prospects with radiation.

The patient undergoes great suffering if no treatment is attempted, and a large fungating growth eventually obstructs food and air passages.

Patients may be better off, after laryngectomy/after pharyngo-laryngectomy, in those cases suitable for surgery.

1913: Trotter's Hunterian Lecture describes the operation of lateral pharyngotomy using transverse skin flap to reconstruct part of the cervical œsophagus.

The use of the transverse neck skin flap has certain limitations:

(1) It may be used only for fairly limited excisions.

(2) There is a risk of sloughing at its free end, since it is orientated across the path of normal blood supply.

(3) The pre-operative use of radiation enhances the risk of skin flap necrosis.

(4) There is skin shortage all the time, i.e. there is usually an attempt to provide lining and cover with this flap.

Laryngectomy lays open the pharynx and upper œsophagus. It is sometimes feasible to repair this at the primary operation, but on occasions an œsophageal fistula remains open in front which requires addition of skin for closure. There is a permanent tracheostomy.

Total pharyngo-laryngectomy leaves three openings, one above into the oro-pharynx, and two below the stumps of œsophagus and trachea.

The patient constantly dribbles saliva from the oro-pharynx. Following the excision, the following procedures may be followed:

(1) Closure of neck wound by replacing skin flap or flaps over prevertebral tissues, and long-term reconstruction of cervical œsophagus using flap skin for lining and for cover.

(2) Immediate reconstruction of cervical œsophagus using skin graft on a tube.

(3) Combination of (1) and (2)—either part skin graft and part flap for lining, or early preparation of adjacent skin flaps for lining.

(1) Long-term reconstruction takes weeks. Meanwhile, patient dribbles constantly down the front of the neck from the oro-pharyngeal opening and is generally miserable. There is during this time the risk of inhalation bronchopneumonia. Once completed, the flap-lined œsophagus requires no post-operative care, and there is no risk of contracture.

(2) Immediate reconstruction of œsophagus, using Thiersch graft on a tube, requires meticulous technique for success. It has the advantage of one operation for excision and reconstruction, without the dribbling interval. Z-plasty flaps give better exposure than transverse or H flaps, and can be adjusted on each other when sutured to give close apposition to the underlying tube and graft. Heavy pre-operative radiation prejudices vitality of any skin flap.

Hæmostasis must be perfect, and the graft-covered tube must fit snugly, and head and neck fixation must be good. It is best done in the thin type of patient.

The graft-tube is inserted within lumen of œsophagus and the graft-tube should be removed *between two and four weeks*, and not left for as long as six months.

There is a risk of general contracture of the graft-tube.

There is a risk of constriction at junction of graft with oro-pharynx above, and of graft with œsophageal stump below, but although this may be apparent in X-rays it does not always interfere with the swallowing of food.

Follow-up with barium swallow and X-rays should be undertaken to outline the lumen of the new œsophagus.

Bougies have not been used for dilatation of new œsophagus in any cases shown—these cases are on normal diet, and have gained from 1–2 stones in weight.

The need for meticulous technique has been mentioned.

This involves: careful hæmostasis in the field of dissection; careful fixation of graft to tube and of skin flap over the tube and restriction of head and neck movements.

In my experience, immediate reconstruction by a graft on a tube should not be done where a tracheotomy is already in existence. The risk of infection is too great and the result may be breakdown of the whole graft with the possibility of inhalation bronchopneumonia.

(3) A disadvantage of (1) flap-skin reconstruction lies in the weeks required to prepare the flaps, and to bring them into appropriate position.

Despite the speed of (2) skin graft on a tube method, there is the risk of contraction of the skin graft lining, and the need over several months for dilatation with bougies. There is also the risk of ulceration of the tube through the graft if the tube is left too long.

Given, if possible, some weeks before the date of pharyngo-laryngectomy, it would be possible to prepare skin flaps, so that on the day of excision of the larynx the cervical œsophagus could be

reconstructed, with flap-skin for lining, complete in the upper part, and forming a gutter in the lower part of the œsophagus. This lower gutter could be completed two weeks later.

The patient would have only two weeks in the dribbling stage, but have flap-skin instead of skin graft for lining. The disadvantage is that of several operative stages, offset, however, by freedom from need for dilatation in the post-operative period.

Diet.—.Adequate balanced diet is fed through a Jacques stomach tube during the convalescent period until food can be taken by mouth.

Speech.—These patients are, of course, deprived of speech as a result of surgery, and this fact should be explained to them before operation.

After-treatment includes lessons from the speech therapist in œsophageal speech, which most patients find difficult after total pharyngo-laryngectomy, but easier after laryngectomy.

An artificial larynx may be used.

A film was shown demonstrating total pharyngo-laryngectomy with immediate reconstruction of cervical œsophagus, by a Thiersch graft on a tube.

3 cases were demonstrated (2 Sir Stanford Cade and 1 Mr. G. Livingstone) on whom reconstruction of cervical œsophagus had been performed.

1 case—long-term reconstruction by skin flaps for lining and cover.

2 cases—immediate reconstruction by Thiersch graft on a tube.

Mr. V. E. Negus was of the opinion that a limited operation with preservation of the larynx was only practicable in a few cases where the growth was limited to the posterior wall of the cricopharyngeal fold, or in cases of chronic hypopharyngitis in which malignant changes were thought to be present or impending. Other cases required removal of the larynx together with the lower part of the pharynx, the upper end of the œsophagus, and usually four rings of the trachea.

Primary repair gave very great advantages if it could be carried out, since the whole operation could be completed in three hours, with little discomfort to the patient in after-treatment.

The first case he had operated on was with Professor Charles Robb, when a plastic tube was placed under the skin flaps, but without skin grafting. A second operation was required.

In other cases Mr. Negus had used a plastic tube covered with a skin graft and, on the advice of plastic surgeons, had left the tube in for six months. Unfortunately there was a tendency to the formation of strictures, which required subsequent plastic repair.

He was not in favour of a U-shaped flap as this seemed to give a greater chance of recurrence.

Mr. Ronald W. Raven: I have a series of 18 patients with carcinoma of the hypopharynx and cervical œsophagus; the majority had advanced disease, 50% had cervical lymph node metastases and some had been pronounced untreatable. These were suffering severely from dyspnœa, stridor and dysphagia and some had received irradiation treatment but the disease was extending. I performed the following operations; laryngo-œsophago-pharyngectomy 12 patients, laryngo-pharyngectomy 4 patients (in 1 an end-to-end pharyngeal anastomosis was done), pharyngectomy with conservation of the larynx 2 patients. There was no operation mortality; the longest survival period is thirty-four months; 12 patients have lived one year and more after operation. A bilateral block dissection of the cervical lymph nodes must be done, but 1 internal jugular vein is conserved. I do not advise pharyngectomy with conservation of the larynx as there is a greater risk of recurrence. For patients who have had irradiation there are special difficulties in reconstruction of the pharynx; for these I have used acromio-pectoral tubed pedicle skin grafts successfully.

Mr. R. G. Macbeth said that it was evident from what had been stated that day and from his own experience, that in the task of reconstruction of the pharynx, either primary or secondary, the help of the plastic surgeon was of the greatest possible value. He thought that experience had shown that it was better from the point of view of voice and swallowing, if possible, to retain a pharyngo-œsophageal strip, which meant a two-stage operation. It appeared to him, however, that the primary reconstructive operation had an important place, provided that the total amount of treatment given to the patient could be shortened, as compared with the two-stage operation. He felt that one should try to remove the plastic tube as early as possible, and he had done so on the sixteenth post-operative day. It was important to use as large a tube as possible and transverse fixation of it by nylon sutures, to which Mr. Reidy had drawn attention in his film, was essential.

It was advisable to perform a radical neck dissection at the time of the operation, whether glands were palpable or not pre-operatively.

Mr. Geoffrey H. Wooler: The surgical treatment of this condition should be completed at one operation. The mediastinal as well as the cervical lymph nodes should be excised, even if this necessitates dividing the sternum.

I have only one such case to describe which Mr. T. McM. Boyle and I operated on together. It was a carcinoma of the pyriform fossa which had spread around the entrance to the œsophagus. By mobilizing the œsophagus as far as the aortic arch we were able to anastomose it to the pharyngeal mucosa. The patient made an uninterrupted recovery and was swallowing by mouth two weeks after the operation.

Section of Orthopædics

President—PHILIP WILES, M.S., F.R.C.S.

[*February* 5, 1952]

SYMPOSIUM ON SARCOMA OF BONE

[*Abstract*]

Sir Harry Platt: (1) The speaker's contribution was based on a review of a personal series of 218 fully documented "sarcomas" of bone studied during the past thirty years:

Osteogenic sarcomas	127
Extra-periosteal sarcomas	39
Ewing tumours	24
Sarcoma in abnormal bones	23
Malignant giant-cell tumours	5

(2) Reference was made to the importance of classifications. Two types of classification were useful. (*a*) For the purpose of a registry; the essentials of such a classification were comprehensiveness and fluidity. (Note the 1939 classification of Ewing.) (*b*) For diagnostic purposes, a simple grouping was needed and should be based on the recognition of *clinical* types of tumour.

(3) As an aid to diagnosis in any suspected tumour, the primary distinction between *extra-osseous* and *intra-osseous* lesions was of fundamental significance. The ultimate diagnosis in sarcoma of bone represented a *total* appreciation of the significance of data derived from (*a*) clinical observations; (*b*) radiographic changes—the reaction pattern of bone as a substance rather than as a tissue; (*c*) biopsy findings—both naked eye and histological.

(4) Special difficulties in diagnosis could be encountered in all the main clinical types of bone sarcoma, but, on the whole, confusion with non-neoplastic lesions—inflammatory, dystrophic, granulomatous or parasitic—was a temporary difficulty.

(5) The sarcomas of bone in general still represented one of the most lethal forms of malignant disease, but the outlook was not as gloomy as was formerly believed. The highest survival rate was seen in the *chondrosarcoma* group, and more particularly in those tumours which represented the malignant transformation of a simple chondroma. (10 out of 19 five-year survivals in the speaker's series of 127 osteogenic sarcomas.) *Ewing's* tumour offered the poorest prognosis (lantern slides illustrating 2 cases of five-year survival were presented). The *extra-periosteal* sarcomas in the speaker's series (39 cases) contained a relatively high proportion of short survivors. Prediction of survival periods in given tumours was at present a haphazard affair. The histological grading of the malignant cells might in the future make for greater precision.

(6) The speaker deprecated delay in the radical ablation of a bone sarcoma once the diagnosis had been settled. He emphasized the human side of the problem—the need to restore the patient to normal pursuits as soon as possible. In tumours in certain situations the conservative operation of resection was feasible, but amputation of the limb still remained the basic mode of attack. Reference was made to the role of the hindquarter amputation which had removed many tumours of the bony pelvis and upper end of the femur from the inoperable class.

Sir Stanford Cade: *Osteogenic Sarcoma.*

Nomenclature.—The speaker's remarks were based on a study of 98 cases of osteogenic sarcoma. The term "osteogenic sarcoma" was first used by Ewing more than thirty years ago and was meant to convey that the tumour was derived from bone cells or cells destined to become bone in the normal process of development, namely the *osteoblasts*; it was therefore a tumour derived from bone or bone-forming tissue.

The terms "periosteal sarcoma" and "endosteal sarcoma" were used before 1920, that is before the formation of the Bone Tumour Registry of the American College of Surgeons. To-day they may be considered old-fashioned as they do not indicate distinct entities of neoplasm, and, in fact, pursue a similar course. He would prefer the term *osteosarcoma* if the term osteogenic sarcoma were no longer in favour.

But even the Registry of Bone Sarcoma describes six varieties under the heading of osteogenic sarcoma and two varieties under the chondroma series and the following terms are used:

(1) Osteogenic series (Osteogenic sarcoma)	(1) Medullary and subperiosteal (2) Telangiectatic (3) Sclerosing (4) Periosteal (5) Fibrosarcoma: (*a*) Medullary (*b*) Periosteal (6) Parosteal, capsular
(2) Chondroma series ..	(1) Chondrosarcoma (2) Myxosarcoma

These terms did not in his experience denote definite and distinct entities of tumours—but merely variants in one clinical disease entity. On reflection, it was obvious that the terms endosteal or medullary subperiosteal, periosteal, parosteal and capsular were anatomical terms, "telangiectatic" and "sclerosing" were physiological terms and the terms fibrosarcoma, myxosarcoma and chondrosarcoma were histological terms. Thus the first group indicated which way the tumour spreads—within the bone or through it; the second group denoted osteolytic or osteoblastic activity; and the third group denoted certain histological features—namely the presence in preponderance of fibrous tissue, cartilage or myxomatous degeneration.

From the clinician's point of view there was no difference between these types or varieties as regards their clinical course, the response to treatment and the prognosis. It was, however, of interest in connexion with the term "chondrosarcoma" to distinguish two types: the "primary chondrosarcoma", which was, in fact, a variant of osteogenic sarcoma containing a lot of cartilage, and the "secondary chondrosarcoma", which was a metaplasia in a pre-existing, generally old-standing benign chondroma. This distinction was of practical interest as the clinical history and the age incidence of these two groups were different.

Significance of delay in treatment.—It was commonly acknowledged that in the case of the common varieties of epithelial cancer—stomach, rectum, breast—delay in treatment materially affected the prognosis. Thus early resection of epithelial cancer was considered of great importance and in fact was so. This does not seem to be the case in osteogenic sarcoma. From an analysis of 400 cases of bone sarcoma, Ferguson (1940, *J. Bone Jt. Surg.*, **22,** 92, 916) came to the conclusion that amputation should not be done at an early stage of the disease. He divided his series in two groups, those with early amputation (within six months of the onset of the disease) and delayed amputation (beyond six months), the former showed only 5% of freedom from symptoms for five years; the latter, 34% of freedom from symptoms for five years.

Site and time of appearance of metastasis.—It is generally recognized that the lungs take pride of place as regards the site of metastasis. It is also fairly well known that skeletal metastases occur in osteogenic sarcoma. It requires, however, some emphasis that lymph gland metastases are not infrequently seen—thus enlarged glands in the groin, the axillæ and the neck are found in a number of cases.

The time of development of metastases is also of interest. The earliest to develop are the lymph-node ones, within six months of the onset of the disease; the latest, the skeletal, within two to four years. In the common site—the lungs—they recur as a rule within twelve to fifteen months. The metastases mimic with accuracy the subvariety of the primary growth. In the periosteal group with sun-ray spicules, skeletal metastases are of similar type. In the bone-forming ossifying tumours the glandular and pulmonary metastases show marked ossification.

Choice of Method of Treatment.

Three methods were available:

(1) Amputation, applicable to the primary tumours of limbs but not to those of the head, neck and trunk.

(2) Radiation, applicable in all sites, to primary and metastatic tumours.

(3) A combined radiotherapeutic and surgical treatment.

In the limbs where surgery was feasible the choice—it must be admitted—depended upon the facilities available and the personal ideas and beliefs of the surgeon in charge. In the trunk, head and neck where amputation was not feasible the case ceased to be of a personal interest to the surgeon and was relegated to the radiotherapy department.

The speaker's personal interest in radiotherapy in general, the dissatisfaction with the results of surgery in the majority of patients, the exceptional facilities for all forms of irradiation in his hospital and, above all, the association with friends and colleagues who believed in team work had afforded a great opportunity of testing out the value of the combined radiotherapeutic and surgical method

What evidence was there that radiotherapy had any effect on osteogenic sarcoma? *Clinically:* the diminution in the size of the tumour, sometimes its total disappearance, loss of pain, and return of function. *Histologically:* the changes in the tumour now recognized in other sites as favourable irradiation effects, namely: arrest of mitosis, formation of fibrous tissue, presence of abnormal cells showing monstrosities, diminution of vascularity. *Radiologically:* the changes were, he thought, best described as those usually accepted as the process of healing, i.e. recalcification and re-ossification.

Dosage and Correlation between Dose and Effect.

Sir Stanford Cade's experience could be divided into two periods, the first between 1929 and 1939, when radium only was used (in nearly all cases teleradium) and high tissue doses between 6,000 r and 9,000 r or even 10,000 r were given; and the second period between 1940 and 1950 when conventional X-rays at 200 to 250 kV. was used and much smaller doses up to 3,000 r or possibly 4,000 r given. Looking back at these two periods each of ten years, there was no doubt that the larger doses given by radium were more effective. This observation was, in fact, supported by the experience of the Memorial Hospital, New York.

We were now entering a third period when supervoltage X-rays at 2 million volts was used and a high tissue dose—minimum of 6,000 r was given with hardly any ill-effects on the skin and encouraging in initial results.

Dangers of Irradiation.

Excluding the misfortunes due to poor judgment, poor technique and blind enthusiasm resulting in immediate and remote disasters, attention should be drawn to the fact that therapeutic irradiation, in high tissue dosage, is known to lead after an interval of many years—five to twenty—to the development of osteogenic sarcoma. A considerable number of cases were now on record. Thus osteogenic sarcoma of the ribs following excessive post-operative X-ray therapy for breast-cancer; sarcoma of the jaws following radiotherapy for cancer of the mouth.

Method of Treatment.

Taking into consideration the observation that delay in amputation was not detrimental to the prognosis, that irradiation in high tissue doses is effective and can control the disease, the following routine has been used. Pre-operative irradiation with teleradium or supervoltage X-rays, at a slow rate to a high total dose. Such treatment took six to eight weeks, sometimes more. If radiological and clinical improvement were achieved amputation was postponed for several months, sometimes for several years. If no improvement followed the treatment amputation was performed about two or three months after the termination of radiotherapy.

Finally two other points needed mention:

Biopsy should not be denied to the patient—its dangers were mythical—it often established a diagnosis, it helped to differentiate osteogenic sarcoma from other primary malignant tumours of bone and from metastases. That it was at times difficult to establish a diagnosis even on biopsy was no reason to condemn it.

Ablation of limb.—He preferred disarticulation to amputation. Recurrences in amputation stumps were not unknown.

Professor S. L. Baker, Rheumatism Research Pathological Laboratories, Manchester: *Causes of Difficulty in the Histological Diagnosis of Bone Tumours with some Illustrative Cases.*

Professor Baker said that examination of biopsy material was an important aid to the diagnosis of bone tumours and in difficult cases was often the only method of arriving at an exact diagnosis. Cases which presented difficulty clinically were perhaps rather liable to yield biopsy specimens which were unusual and of more than average difficulty for the histologist.

The causes of difficulty in making a histological diagnosis on biopsy material from suspected bone tumours could be grouped under the following headings:

(1) Inadequate biopsy.
(2) Widespread necrosis and/or degeneration.
(3) Local peculiarities in tumours.
(4) Difficulty in interpreting the histological picture.

(1) *Inadequate Biopsies.*

A biopsy which removed material only from the surface of the bone was often useless because the surface layers often showed a non-specific periosteal reaction over an underlying tumour or inflammatory lesion. A bone biopsy should be undertaken as a surgical operation by an expert and a good sample which extended well into the mass, or into the marrow cavity of the bone where the mass was small, should be removed.

Punch biopsies might give confirmatory evidence in fairly obvious cases; they were not satisfactory in cases of real difficulty.

(2) *Widespread Necrosis and/or Degeneration.*

Widespread necrosis was particularly liable to occur in tumours of the Ewing type and might make histological diagnosis difficult or impossible.

Degenerative changes were common in cartilaginous tumours and might make it difficult to decide the grade of malignancy.

(3) *Local Peculiarities in Tumours.*

Local peculiarities were not uncommon, particularly in malignant tumours, and might result in a biopsy specimen which was not representative of the tumour as a whole.

For example, Professor Baker had encountered 2 cases of osteogenic sarcoma arising in Paget's disease of bone in which there were well-defined areas of tissue containing very numerous osteoclasts. These cells showed very irregular bizarre shapes and were applied to the equally irregular surfaces of numerous small islands of osteoid tissue which were obviously undergoing rapid removal by the very active osteoclastic cells. The appearance in these areas was very unlike the usual osteogenic sarcoma and led to difficulty in interpreting the biopsy picture in the first case. It was, however, quite unlike the picture of an osteoclastoma where the giant cells have a fairly regular rounded shape and show no signs of osteoclastic activity.

Outside the osteoclast-containing areas both tumours showed the histological appearances of osteogenic sarcoma. The significance of this unusual picture in these 2 cases was not certain but it might well indicate Paget change in an osteogenic sarcoma; the essential change in the active stage of the Paget process being a great increase in both osteoclastic and osteoblastic activity such as was seen here.

(4) *Difficulty in Interpreting the Histological Picture.*

(*a*) *An osteoid osteoma of the spine.*—A case of a girl of 15 years who developed signs of an organic lesion of the spinal cord about a year after a fall in the sitting position. A small X-ray shadow was seen on the right side external to pedicles of L 2 and 3 and exploration showed a soft purplish mass about 1 in. in diameter replacing rt. lamina of L 3 but not adherent to the dura. Local removal was carried out as thoroughly as practicable.

Histologically the tumour was quite cellular and showed irregular masses of partly calcified osteoid tissue; there was a considerable amount of osteoclastic activity. In places the osteoblastic tissue had differentiated sufficiently to produce some well-formed woven bone. The tumour was reported as not an osteogenic sarcoma and probably only locally destructive. The patient was well and normally active five years later. On reviewing the histology of this case there could be little doubt that it was an osteoid osteoma. Lewis (1944) described a rather similar mass on the right posterior articulation of D 11 and 12 producing back pain and an X-ray bony shadow. Histologically it was reported as an osteoid osteoma.

(*b*) *Hyperplastic callus.*—Hyperplastic callus may be difficult to distinguish from an osteogenic sarcoma histologically and may also mimic a sarcoma clinically. Very large masses of callus which, during the stage of active proliferation, closely mimic a sarcoma clinically might occur in cases of fragilitas ossium; usually but not always following a fracture; the commonest site being the femur.

A biopsy of such a mass showed at its surface œdematous very cellular tissue containing some remains of striated muscle; proliferation of fibroblasts and chondroblasts were such as to suggest a chondrosarcoma. At a deeper level the tissue was better differentiated and formed cartilage and semi-cartilaginous tissue; deeper still calcified cartilage and well-formed calcified trabeculæ of woven bone were found. This progressive differentiation up to the production of well-formed woven bone trabeculæ served to distinguish such hyperplastic callus from a sarcoma; it was seen in the biopsy material of each of the 4 cases which he had examined histologically.

These enormous masses of callus reached a stage of maturity after a time and the whole mass was then found to have been converted to cancellous bone; this was then gradually absorbed leaving behind, usually, an expanded thin bone (Baker, 1946; Fairbank and Baker, 1948).

Such masses had been mistaken for sarcomas. Sir Thomas Fairbank had drawn the speaker's attention to such a case reported by Battle and Shattock in the *Proceedings* in 1908. The leg was amputated and the specimen, an excellent illustration of which is shown in the paper, was examined by Shattock who recognized its benign nature and described it as a cancellous osteoma. The patient (a boy of 4 years) later developed a similar mass following injury to his remaining leg. The urge to amputate was resisted on this occasion and the mass eventually disappeared leaving behind a thin rather expanded femur. Such spontaneous disappearance was unknown with an osteoma and confirmed that the mass was hyperplastic callus.

(The communication was illustrated by 13 lantern slides.)

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Section of Medicine

President—Sir ALUN ROWLANDS, K.B.E., M.D., F.R.C.P.

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DISCUSSION ON THE MEDICAL TREATMENT OF HYPERTENSION

Professor M. L. Rosenheim: It is just five years since the Section of Medicine last discussed the management of patients with essential hypertension. At that time the discussion was mainly surgical, thoraco-lumbar splanchnicectomy probably then being near the peak of its popularity in this country (*Proc. R. Soc. Med.*, 1947, **40**, 773).

Apart from general care, potassium thiocyanate was the only active line of treatment the physicians could offer, but since then several new lines of attack have been developed. The newer ganglion-blocking drugs, producing a medical sympathectomy, have been widely tried, and are, perhaps, being even more widely used in the treatment of hypertension; the alkaloids of veratrum are under careful investigation while low sodium diets are once again in favour.

I shall not discuss surgical treatment as, being especially interested in the methonium compounds, I have had less recourse recently to surgical aid. Statistics, however, as well as personal observation, leave little doubt that the introduction of surgical sympathectomy was a very definite advance in the treatment of hypertension. The role of adrenalectomy is still experimental.

Before embarking upon a more detailed discussion of low sodium diets and the methonium compounds, I must emphasize that, in my opinion, both these lines of treatment are indicated in a very small proportion of patients found to have hypertension. It is doubtful whether either has much to offer the patient with mild benign essential hypertension. Raised blood pressure is frequently discovered at routine medical examination and would in many cases have remained symptomless for years. In many patients with mild hypertension, such symptoms as occur are largely due to anxiety. There is, at present, no adequate evidence that specific therapy with diet or drugs prolongs the life of patients with mild hypertension, there is plenty of evidence that such treatment may turn them prematurely into invalids. With both hexamethonium and low sodium diets, the blood pressure returns to its previous high level when the treatment is stopped, and neither is a simple form of treatment which a patient with mild hypertension or his doctor could contemplate continuing over years.

The medical treatment of the mild case of hypertension remains unaltered. It consists first of all in reassurance, in the better organization of the patient's life, at work and at home, in the reduction of obesity and, often, in mild sedation. The patient needs to be seen at regular intervals and to receive a helping hand over the various physical and emotional hurdles which so often precipitate symptoms in the hypertensive.

Low Sodium Diets

Low sodium diets have been repeatedly advocated for the treatment of severe hypertension during the past half-century. There can be no doubt that strict sodium restriction, to a daily intake of less than 200 mg. of sodium or 0·5 gramme of salt, will reduce the blood pressure in a majority of cases. This is the basis of the Kempner rice diet, and this diet is a very effective method of maintaining a rigid low sodium intake. However, other low sodium diets can be prepared and are claimed to be as effective. The addition of sodium-free protein certainly does not put up the blood pressure once it has fallen, and a more varied diet prevents the usual loss of weight. There are two reasons why low

sodium diets in the treatment of hypertension tend to fall into disrepute. The first is that the sodium intake is often insufficiently reduced, the second that patients will rarely tolerate severe sodium restriction for long. Half-measures are useless. If the hypertensive patient is not on a really low intake, he might as well be on a normal diet.

The treatment requires the full co-operation of the patient, who must be persuaded of the necessity for the diet and encouraged to persist with it. This is easier in patients with severe hypertension, who more readily appreciate the benefit that results from it.

In a clinical trial of the Kempner rice diet, carried out at various centres on behalf of the Medical Research Council, Kempner's claims were confirmed[1]. It was found that a considerable fall of blood pressure could be expected in about 70% of patients with either essential or chronic renal hypertension, provided that they adhered to the regime. The diet produces marked symptomatic relief of headaches and dizziness, and reduction in heart size and improvement in the electrocardiogram and in the eye-grounds were also observed. The low sodium intake also relieves œdema and aids patients with left ventricular failure. The only real contra-indication to the diet is the presence of renal failure, for patients with renal damage are often unable to control the loss of sodium in the urine and tend to stand sodium restriction badly. Severe depletion and even death may follow. Similar sodium depletion may occur if mercurial diuretics are used in patients on the diet.

I am convinced of the beneficial effect of the rice diet and of other low sodium diets, but unfortunately they are poorly tolerated by the patient and difficult to manage in the home.

Hexamethonium

Of the various drugs that block the transmission of sympathetic vasoconstrictor impulses at the ganglia or antagonize the effect of adrenaline or sympathetic stimulation at the nerve endings, hexamethonium, at least in this country, has proved the most effective and has already gained a place in the treatment of hypertension. Others such as tetra-ethyl-ammonium salts are too short in their action; some, like Priscol, are more effective in the treatment of peripheral vascular disease and have little hypotensive action, while others, such as Dibenamine, are difficult to administer and too toxic to permit of regular use. Hexamethonium is far from perfect and the search for other and better drugs has been stimulated by the results so far obtained.

Hexamethonium blocks the transmission of impulses through both sympathetic and parasympathetic ganglia and, while the first action is beneficial to the hypertensive, the latter produces certain side-effects such as paralysis of accommodation, dryness of the mouth, constipation and distension (and sometimes full paralytic ileus). Difficulty with micturition occasionally occurs. Fortunately these side-effects are rarely severe, and they usually do not appear until an effective therapeutic dose is reached. They may, however, prove so troublesome that the dose has to be reduced or the treatment abandoned. Occasionally they occur dramatically, especially in patients being treated by mouth. We are trying the effect of pilocarpine on these side-effects. The bowels require attention in every patient treated and constipation should, if possible, be avoided. Neostigmine appears of value in dealing with abdominal distension.

The fall of blood pressure in the hypertensive is largely due to the removal of abnormal vasoconstrictor tone, but it is also partly postural. Normal or hypertensive subjects develop marked postural hypotension under the influence of hexamethonium. This postural hypotension, with its giddiness and faintness, may prove troublesome and most patients have to lie down for about an hour after the injection of the drug. Postural hypotension is a sign of effective action and is not a toxic effect. Much of the benefit of the drug may, in fact, result from the additional lowering of the blood pressure in the sitting or standing position.

A possible danger of producing widespread vasodilatation is that blood flow through pathologically narrowed arteries may fall and thrombosis result. Cerebral and coronary thromboses might thus occur and have, in fact, been reported. These, of course, may happen in any severely ill hypertensive patient and it is difficult to decide how far hexamethonium is responsible. I have used the drug with success in a patient who had had several cerebral thromboses before treatment started, and have continued to give it to a patient with malignant hypertension who developed a hemiplegia while under treatment. I am, perhaps, more cautious in the presence of severe coronary artery disease.

Hexamethonium salts can be given orally, by subcutaneous, intramuscular or intravenous injection. The salts are poorly absorbed from the gut and the effective dose by mouth is at least ten times the parenteral dose. Absorption is irregular and varies with a number of factors; sudden increase in rate of absorption may precipitate severe side-effects. Used by mouth the dose of the anion is large enough to be important, and care must be taken if the bromide is used. We have a number of patients on regular oral dosage, but prefer the subcutaneous route of administration.

The drug is not metabolized in the body and is normally rapidly excreted. The presence of renal failure, however, markedly diminishes the rate of excretion and small doses may produce prolonged

[1] *Lancet*, 1950, ii, 509.

effects. This is one reason for exercising great care in the treatment of patients with a high blood urea. There is another. In hypertensive patients with normal or only slightly impaired renal function, the low blood pressure produced by hexamethonium does not appear to cause renal failure, but, in the presence of uræmia, the drug does appear, in some cases, to accelerate the rise of blood urea. Small dosage and close supervision are therefore needed in such patients, but the symptomatic relief of headaches, papillœdema and left ventricular failure makes the use of the drug justifiable.

It is difficult to fix the appropriate dose for the individual patient. In a patient with renal failure as little as 25 mg. per day may prove too much, resulting in constipation and distension, while in patients with severe hypertension and good renal function, we have had to increase the dose to as much as 250 mg. three times a day, subcutaneously, before getting a satisfactory fall in pressure. Tolerance to the drug often necessitates gradual increases of the dose during the early weeks of administration, but a stable dose is usually reached. Tolerance appears more common with oral, but does occur with subcutaneous, dosage.

The effect of any dose can only be judged by repeated readings of the blood pressure in the recumbent and standing patient, and the adjustment of the dosage requires a lot of time. So much so that I am sure that patients should not be started on the drug as outpatients. We usually start by giving a test dose of 25 mg. intravenously or intramuscularly, observing the effect on the pressure. We then start treatment with 25 or 50 mg. subcutaneously two or three times a day and gradually increase the dose until satisfactory control is obtained. We like to have Methedrine or adrenaline handy in case of too dramatic a fall in pressure, but have rarely needed to use them. The blood pressure is taken daily at the same time, some two to three hours after an injection, with the patient resting. A further reading is taken with the patient standing.

Once the dose is established, it requires occasional checking. We encourage our patients to give themselves the injection and we see them regularly. Where possible we get them up to hospital for a day and observe their blood pressure at intervals after an injection. It is difficult to see patients in the outpatient clinic at the height of action of the drug, and casual readings are a poor guide to the effect of the drug. At home, the patient should be seen some two hours after an injection, and lying and standing pressures recorded. We do not aim at maintaining a low pressure or postural hypotension throughout twenty-four hours. We aim at restoring the full lability of the blood pressure with three injections a day. A combination of oral and subcutaneous treatment has been recommended, but I have, as yet, no experience of this to report.

This then is, at present, a difficult line of treatment involving the use of a potentially dangerous drug. Inadequate and poorly controlled dosage cannot be expected to help the patient and overdosage produces marked side-effects. It is clear that such a treatment, a treatment that requires three injections a day, that demands an hour's rest after each dose and that calls for rigorous supervision, cannot be regarded as a useful treatment for the mild case of hypertension. In the severe hypertensive, with a bad prognosis, the treatment is fully justified and very useful.

Hexamethonium has a dramatic effect on certain symptoms in severe benign hypertension; headaches are almost invariably relieved, dyspnœa and dizziness improved and nocturnal dyspnœa may disappear. These are, I think, definite indications for treatment. It is common experience with other lines of treatment that once headaches and dizziness are relieved they may not recur for a long time. Short periods of treatment with hexamethonium in benign hypertension may prove useful in providing symptomatic relief.

It is in patients with malignant hypertension and in those with severe benign hypertension with marked retinal changes or with nocturnal dyspnœa that the drug has its greatest use. We have seen papillœdema improve markedly and exudates and hæmorrhages clear in both essential and renal hypertension. Vision may be saved in such cases. Intense headaches and vomiting that are making life unbearable may be dramatically relieved and both acute and chronic pulmonary œdema improved. A number of patients admitted with severe dyspnœa due to chronic pulmonary œdema have obtained immediate relief. In such cases the initial dose should be small, for, if renal failure co-exists, a prolonged fall of pressure may occur. Hexamethonium is also of value in the treatment of cerebral œdema with coma, but I have little experience of this.

It is in such patients, with severe hypertension and a poor prognosis, that every attempt must be made to continue regular therapy and I have no doubt that the life of such patients can be markedly prolonged.

Hexamethonium therapy is still experimental—we need a drug that has a more potent effect on the sympathetic than on the parasympathetic ganglia, and one that is either regularly absorbed when given by mouth, or long-acting on injection. With the present drug, we need to explore various methods for controlling the side-effects. However, with all its difficulties, the drug has already proved of very great value in the treatment of severe hypertension.

Dr. Ralph Kauntze: It is regrettable that there is, as yet, no satisfactory treatment of systemic arterial hypertension, in part because we remain ignorant of the essential mechanism. Whereas in

essential hypertension the blood pressure is peculiarly labile and amenable to such procedures as sympathectomy, spinal anæsthesia, pyrogens, diet and drugs, that response is too often temporary and in the case of the hypotensive drugs, there is the added feature of unpleasant side-effects. None the less, experience with these measures has added something to our knowledge of the ætiology and in a proportion of patients the results, both objective and subjective, have been mildly encouraging. I shall only discuss treatment with the veratrum group of drugs, principally Veriloid, of which I have had some eighteen months' experience.

That veratrum viride would lower the blood pressure has been known for many years (Douthwaite, 1928), and although used in puerperal eclampsia (Bryant, 1935), the difficulties in obtaining preparations of uniform potency for long precluded continuous treatment. In 1948, Fries and Stanton reported on the effects of veratrum viride in hyperpiesia, and a year later Stutzman *et al.* (1949) produced by fractionation a stable, reproducible and potent mixture of ester alkaloids, to which the proprietary name of "Veriloid" was applied. This fraction contained none of the potent alkaloids previously isolated from veratrum. Standardization has been by bio-assay of the vasodepressor effect in dogs, a more reliable method than the measurement of lethality. Certain of the hypotensive alkaloids have been isolated in pure form, among which are germitrine and germidine (Fries *et al.*, 1950), thereby allowing standardization by weight. Their action, dependent on the ester group, is similar to veriloid and veratrum; the side-effects are, unfortunately, no less.

Action

The main effects of veriloid, both in man and dog, are hypotension, bradycardia and emesis. Veriloid acts upon the afferent vagus and central nervous system direct, giving rise to dilatation of arterioles in muscles, skin and splanchnic area together with constriction of the veins (Stutzman *et al.*, 1949). Dawes *et al.* (1951) rate the von Bezold reflex (von Bezold and Hirt, 1867) which is mediated through vagal receptors in the myocardium, of high importance in the production of hypotension; yet in man the hypotension from intravenous infusion of veriloid precedes slowing of the pulse, and atropine, whilst eliminating the bradycardia, causes only a slight rise of blood pressure (Fig. 1). Bilateral cervical vagotomy in the dog, though it abolishes the bradycardia, does not quantitatively alter the hypotension (Stutzman and Maison, 1950), and isolated perfusion of the head of the dog yields profound hypotension, but no bradycardia (Stutzman *et al.*, 1951). Finally, in the dog if veratrum is confined to the body, hypotension matches bradycardia, and can be prevented by anything which blocks the bradycardia. For these reasons, Maison (1952) considers the hypotension mainly of central origin. None the less, where slowing of the pulse is present, it seems justifiable to assign some part in the hypotension to the von Bezold reflex.

Bradycardia is vagal in origin and abolished by atropine; only in one patient has it been so pronounced as to cause treatment with veriloid to be discontinued. Emesis or nausea may be primarily central or hypotensive in origin. Local irritation of the gastric mucosa is considered unimportant by Swiss *et al.* (1951), and in the dog, intravenous injection produces no local intestinal stimulation prior to emesis (Gourzis and Bauer, 1951). On intravenous injection in man, nausea when present succeeds the fall in blood pressure.

Veriloid intravenously in a dose of 1 microgram/kg./minute for ten minutes (Fig. 2) will lower the blood pressure considerably in almost all hypertensives, except in the preterminal malignant phase. For this reason it can be used effectively in the treatment of hypertensive encephalopathy, and probably puerperal eclampsia, although in the latter I have had no experience. After preliminary control by the intravenous route it is often possible to continue treatment orally. Even patients who appear resistant to the drug orally are susceptible to intravenous infusion (Fig. 3). However, the parenteral route is unsuitable in a chronic disease, which may be in the symptomless stage, and if it is conceded that hypertension is not simply an adjustment to organic vascular disease, and that to lower the blood pressure is justifiable provided no ischæmia results, then some preparation must be found effective by the mouth, the action of which is not too short-lived and which is free from objectionable side-effects. Unfortunately, no such preparation is at present available. With veriloid, the difficulties lie in the vagaries of intestinal absorption and the side-effects. Veriloid in a single dose, fasting, yields its maximal effect between three and five hours after ingestion (Fig. 4); but the rate of absorption varies from day to day in the same individual. Food taken after veriloid will hasten absorption and toxic symptoms may ensue. In consequence the drug should be taken directly after meals. With two doses spaced at seven hours the blood pressure may be controlled during ten hours (Fig. 5), but for a continuous hypotensive effect usually three or four doses in the day are necessary, and the spacing should be at intervals of not less than four and a half hours. With the four-dose schedule, the last dose should be given at 10 p.m. or later. The larger doses are best given after breakfast and before retiring. The preliminary ration should be 8 mg. in four equal doses, a lower level being usually ineffectual. After three days if the blood pressure remains unchanged, the morning and night doses should be increased by 1 mg. each, thence the middle doses raised. Subsequent increases should be gradual, for the margin between a slight and profound hypotensive effect is critical; because of cumulation the times of administration must be rigidly observed. Toxic symptoms appear as an

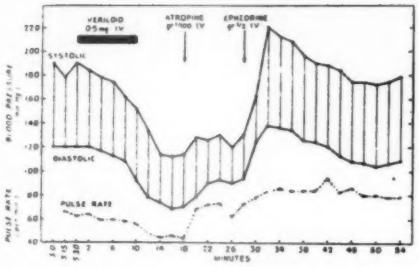

FIG. 1.—The effects of atropine and ephedrine on the relative hypotension from intravenous veriloid.

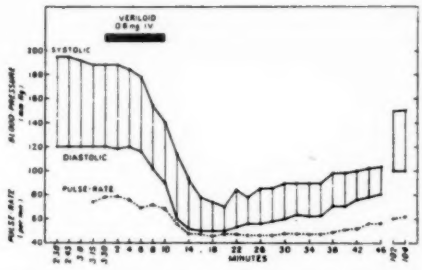

FIG. 2.—The effect on the hypertensive blood pressure of veriloid 1 microgram/kg./minute, i.v., for ten minutes.

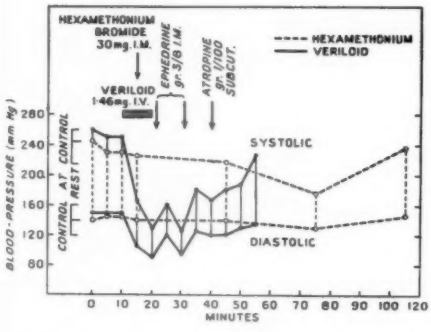

FIG. 3.—The response to veriloid i.v., where 42 mg. daily by mouth produced no constant effect.

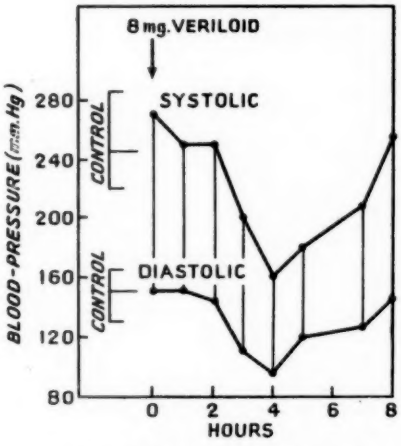

FIG. 4.—The effect of a single dose of veriloid fasting.

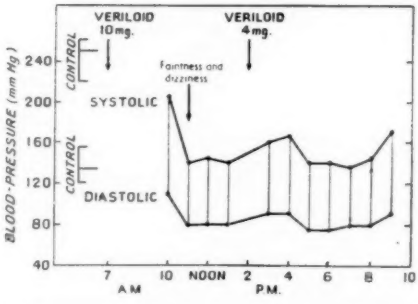

FIG. 5.—Control of blood pressure during ten hours from two doses of veriloid by mouth.

emptiness behind the lower sternum, at times amounting to pain of a burning character, then salivation and choking, hiccough, nausea, recurrent vomiting at five to ten minutes, lasting up to an hour and a half; probably mediated through the vagus and not necessarily accompanied by any profound fall in blood pressure or pulse-rate. Finally, coldness in the periphery, vomiting and collapse, the results of circulatory failure. To some degree these side-effects have been present in every patient, even with veriloid 12 mg. a day; they are the main impediment to successful therapy. Combining each dose of veriloid with a small dose of phenobarbitone has been the most helpful procedure in raising the threshold to nausea, and this combination is now routine. Banthine is reported as valuable in the control of nausea; the atropine group and the antihistamines have proved disappointing. When slight, recumbency will often ward off these symptoms, but if nausea is prolonged or vomiting occurs then the subsequent dose should be halved. Ideally, the patient should be in hospital until stabilized, and this is essential where the dosage is large. Even in the successful response the dosage may need repeated adjustment, either more or less sensitivity occurring after months of treatment; often between the third and fourth weeks the dose will need lowering. If at any time hypotension is profound, then ephedrine i.m. will readily reverse this.

I shall illustrate these features by individual cases.

A single woman, aged 39 (Fig. 6), with chronic nephritis and hypertensive encephalopathy has been under treatment for over a year. The control of blood pressure and freedom from symptoms have been most satisfactory. The dose of veriloid has been small and needed only slight adjustment, nausea has not been troublesome since phenobarbitone has been given concurrently. After nine months, severe urticaria caused the omission of veriloid and phenobarbitone, the blood pressure rose and symptoms reappeared. Resumption of veriloid reduced the blood pressure. Unfortunately, a further attack of urticaria has caused the temporary omission of veriloid. The urinary sediment remains unchanged, the blood urea is now 57 mg. per 100 ml.—an increase of 10 mg. in the past year.

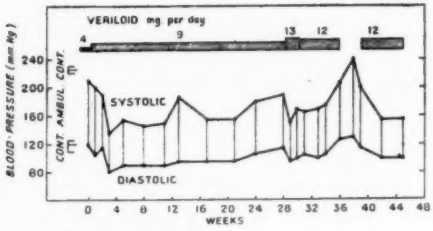

FIG. 6.

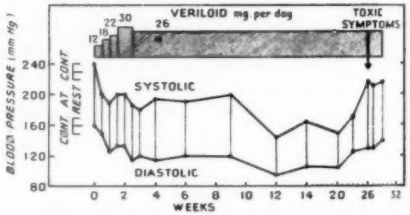

FIG. 7.

An editor, aged 41 (Fig. 7), with essential hypertension was admitted to hospital a month after a cerebral thrombosis, the objective evidence of which disappeared in three days; the presenting complaints were of fatigue and effort dyspnœa. His response to veriloid was excellent up to the twentieth week of treatment, since when he has been working at considerable stress, the blood pressure has mounted, and at times toxic symptoms have been temporarily troublesome. This sequence of improvement in health, extension of activity and rise in the blood pressure is a not uncommon occurrence. He has been throughout on a low sodium diet, at the week-ends his doctor has noted persistently lower values than those recorded as an out-patient. The left heart strain pattern in the cardiogram was unchanged after six months. There is an aortic diastolic murmur, presumably a "hyperdynamic leak", which remains audible with diastolic levels of 95–90 mm.Hg so that permanent stretching of the ring seems likely.

A tyre fitter, aged 41 (Fig. 8), with essential hypertension and severe headaches has been treated as an out-patient during seven months with relief of headache and control of blood pressure, coincident with which he has increased the extent of his work, which is not inconsiderable. With the omission of veriloid the blood pressure, although it rose, did not quite reach its previous systolic level. His sole complaint has been of impotence, which his wife attributes to veriloid.

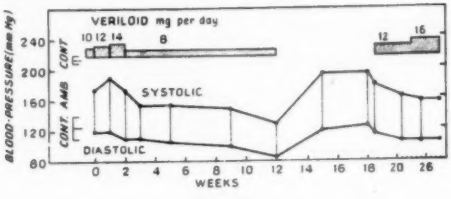

FIG. 8.

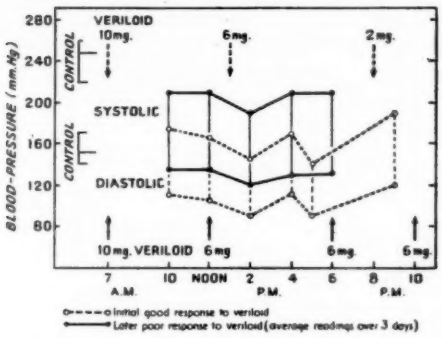

FIG. 9.—Comparison of initial and subsequent responses to veriloid orally, in the presence of pylorospasm.

Although the early response may be satisfactory (Fig. 9), later even a larger dose may yield less good results, as in this patient with malignant hypertension, in whom pylorospasm interfered with absorption. In this connexion one patient developed an acute gastric ulcer whilst under treatment.

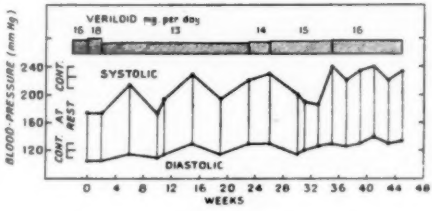

FIG. 10.

This patient, a male confectioner, aged 46 (Fig. 10), had been unable to work for six months on account of bursting headaches. There has been some lowering of the blood pressure, but the levels have gradually crept up. He had much symptomatic relief and was able to resume work, until three months ago, when he was readmitted to hospital with left ventricular failure. The reappearance of presystolic triple rhythm when veriloid was omitted was quite striking. The retinæ improved from grade IV but slight papilloedema remained, latterly the changes have become gross. This partial lowering of blood pressure has had no effect on the outcome of his hypertension, yet my impression is that deterioration has been slower than would otherwise have been expected.

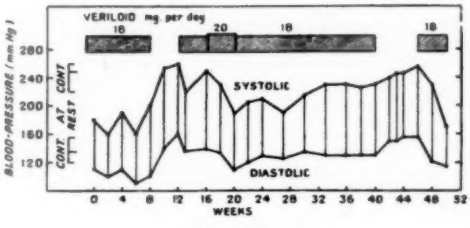

FIG. 11.

(FIGS. 1–11 are reproduced by courtesy of the *Lancet*.)

A further patient, a portly and plethoric builder, aged 62 (Fig. 11), with essential hypertension has been under treatment for a year. On both occasions withdrawal of veriloid has been attended by some increase in blood pressure, headache and cardiac asthma. A return to treatment has brought relief, comparable to that after venesection.

Results

In the past eighteen months, Dr. John Trounce and I (1951) have used veriloid orally in the treatment of 23 patients with hypertension; 15 with essential, 3 each with chronic pyelonephritis and malignant hypertension and 2 with chronic nephritis; none has had a diastolic pressure less than 120 mm.Hg at complete rest, and only one has been free from symptoms. In other words this is a group, in which death within five years would be the usual expectation, and where assessment of therapy on the course of the disease is more rapid. No attempt has been made to keep the patient normotensive. The results *qua* blood pressure and symptoms have been good in 6 (25%) and fair or temporary, with symptomatic relief in 12 (52%). There is no doubt that the longer one follows the "good results" the less good will these become, for these are all severe hypertensives and the disease advances. Treatment in the early hypertensive may conceivably arrest or delay those progressive changes which at a later stage seem inevitable: but here the burden of daily medication on an individual who admits to no symptoms is hard to bear and continuity of treatment is unlikely. There are times when one yearns for the finality of surgery, that is as regards continuity of treatment. In the second group, objective assessment is most difficult, symptoms reappear with the substitution of placebos, but of course the patient is usually aware as to whether he is receiving veriloid. Although the effect on blood pressure may be relatively slight, yet the invalid may for a time return to work; where encephalopathy is frequent, the patient will endure recurrent and severe side-effects rather than the encephalopathy.

Veriloid is not sympatholytic and postural hypotension does not occur unless the dose is excessive; nor are the pressor responses to acute hypotension obliterated, but these overshoots are at a lower level, and the improvement in dyspnœa, disappearance of alternation and triple rhythm and the loss of facial mottling and headaches, suggest that some lowering of the load on heart and cerebral vessels is as beneficial as the reduction in venous pressure in certain cases of congestive cardiac failure. I have seen no reversion to normal in the left heart strain pattern of the cardiogram on chronic administration. Cerebral function as judged objectively is often considerably improved. In 2 patients, cerebral thrombosis has occurred under treatment and in 2, cerebral hæmorrhage has ended life. I am doubtful whether therapeutic hypotension has any considerable bearing on the development of cerebral thrombosis. Retinal hæmorrhage and œdema resolve slowly unless the diastolic level is below 95 mm.Hg; deformity of the arterial wall persists. In chronic renal insufficiency, I have not noted further impairment of function which could fairly be attributed to the hypotension. Fries *et al.* (1949) have shown that the cardiac output and renal and limb flows remain adequate after the initial sharp fall in blood pressure following intravenous infusion of veriloid.

Conclusions

Veriloid intravenously will lower the blood pressure in almost all hypertensives with the exception of the preterminal malignant and probably the chromaffinoma; by mouth about 60% of hypertensives will respond, yet in half of these the therapeutic level is so close to the toxic that use out of hospital is imprudent. In the remaining 20–30% the results may be excellent, but there is no evidence that the progress of the disease is halted, although the tempo may be slowed. Side-effects are the main bar to symptomatic success, and the response to certain pure alkaloids suggests that the toxic and hypotensive principles may be inseparable. For this reason, especially in respect of vomiting, veriloid by mouth is unlikely to be lethal. Phenobarbitone is a useful drug in counteracting nausea. The rigid restriction of sodium in the diet is helpful in potentiating veriloid, but the restriction must be enforced. The main place of veriloid out of hospital is in the treatment of the younger hypertensive.

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JOINT MEETING No. 3

Section of Medicine with Section of Surgery

Chairman—Sir ALUN ROWLANDS, K.B.E., M.D., F.R.C.P.
(President of the Section of Medicine)

[*January* 22, 1952]

DISCUSSION ON HIATUS HERNIA

Dr. F. Avery Jones: *Diagnosis of Hiatus Hernia*

One of the advances in clinical medicine in recent years has been the better recognition of herniation of the stomach through the œsophageal hiatus of the diaphragm, so-called hiatus hernia. The condition is easy to miss when performing a routine barium meal unless the patient is specially postured. It is important, therefore, that the clinician should draw the attention of the radiologist to the possibility of hiatus hernia, which can then be specially searched for. Dr. F. Pygott has supplied the following figures from the radiological department:

TABLE I

X-ray Department. Central Middlesex Hospital

	1947	1948	1949	1950	1951
Hiatus hernia	5	10	14	38	61
Gastric ulcer	158	184	153	134	173
Duodenal ulcer	301	295	416	521	672
Total new barium meals	1,120	1,142	1,472	1,787	1,759

This appreciable increase is due to the greater awareness of the condition by the medical staff, to the introduction of a routine examination of all barium meal patients in a horizontal position and to employing special techniques for demonstrating the hiatus hernia. We are not dealing with a true increase in the prevalence of the disease, which incidentally I believe may be the case with duodenal ulcer, but we are now recognizing cases which formerly escaped detection.

The usual classification is:

(1) Congenitally short œsophagus producing a thoracic stomach.

(2) Para-œsophageal hernia. Here the lower œsophagus remains in the normal position, but a portion of the fundus of the stomach is herniated through the hiatus alongside the œsophagus.

(3) The œsophagogastric hernia, in which the whole of the lower end of the œsophagus and part of the fundus of the stomach is herniated into the chest.

Much of the medical literature on the subject in recent years has been devoted either to the short œsophagus or to the para-œsophageal hernia. Largely, however, owing to the studies of Allison (1951) and Johnstone (1952) it has been recognized that a true congenitally short œsophagus is much less common than had previously been thought and that many patients in this group really had had a primary defect of the diaphragm, causing a reflux or allowing reflux of gastric content into the œsophagus, producing a reflux œsophagitis. Shortening of the œsophagus resulted either from spasm or from ulceration and scarring. The key to the situation today is this recognition of a primary functional defect of the œsophageal hiatus, which leads to a breakdown of the mechanism which normally prevents regurgitation of gastric contents into the œsophagus. This defect may be present at birth, but much more commonly it develops in later life and, in fact, is strictly comparable to other abdominal herniæ such as femoral or inguinal herniæ. The development may be favoured by the loss of elastic tissue, increased laxity of muscles or increased intra-abdominal fat. There may be direct mechanical facilitation of the hernia from increase of intra-abdominal pressure during pregnancy or in the presence of a large ovarian cyst. It is possible that habitual belching may also mechanically favour its development. The hernia may progress in two ways, graphically described by Allison (1951) as the sliding hernia or the rolling hernia. In sliding hernia, which corresponds with the œsophagogastric hernia, the upper part of the stomach slides through the diaphragmatic hiatus with the œsophagus entering at the apex, facilitating a free regurgitation back into the gullet. In the rolling variety there is a preformed hernial sac in front of the œsophagus and the anterior wall of the stomach may roll up into the chest through the hiatus. This corresponds with the para-œsophageal hernia and

as the œsophagus enters obliquely into the stomach there is no free regurgitation back into it. For classification purposes there is a difficulty in that a hernia may be both rolling and sliding. For those who like a numerical classification Belsey (1952) refers to the sliding hernia as type 1, the rolling hernia as type 2 and those which both roll and slide as type 2A. Herniation may be postural and reduced spontaneously when the patient stands up, or it may be fixed and persistent. In considering a case of hiatus hernia one is, perhaps, less interested in classifying it into one of the recognized groups than in recording its size, whether or not it is fixed or reducible, whether there is evidence of œsophagitis radiologically or with the œsophagoscope. Hiatus hernia may cause symptoms at all ages. It may be the cause of regurgitation, vomiting, malnutrition and anæmia in infants and indeed many cases which formerly died from intercurrent infection are now being recognized and successfully treated. In adults, however, it is predominantly a disease affecting women. It may occur occasionally during the later months of pregnancy, but its main incidence is after the reproductive period of life. There are at least three times as many sufferers among women as among men. This sex ratio, however, does not hold for those who have added complications of œsophagitis, and here the sex ratio is equal. I do not propose to present a detailed analysis of our own cases as this will be done in due course by my colleagues, Dr. V. Edmunds and Dr. G. Scott and Miss M. A. M. Bigby, who are making a special study of them. Symptoms may be absent or minimal, but at the other end of the scale the patient may be completely crippled and driven to desperation from incessant pain or dysphagia. Four components may contribute to the clinical picture. There may be a mechanical factor with symptoms from distension of the œsophagus or from pressure on it from a herniated gastric sac, mediastinal pressure may give rise to dyspnœa, palpitations or cough and diaphragmatic irritation may cause spasm with pain or hiccough. Secondly, symptoms may be inflammatory in origin from œsophagitis or ulceration of the œsophagus; thirdly, symptoms may arise from an associated peptic ulcer, either within the hernial sac or at the ring of constriction or elsewhere in the stomach. Such ulceration may be responsible for the usual complications that may occur with ulcer. Fourthly, blood loss may be a prominent feature, not only a frank hæmatemesis, but also a low-grade, slow loss of blood, producing an iron deficiency anæmia. Retrosternal discomfort or pain associated with change in posture is a salient feature and the severity of such symptoms will depend on the presence or absence of œsophagitis. The patient notices retrosternal pain or discomfort and acid fluid may rise into the mouth on bending, stooping, sitting down in an upright chair or on lying down. Bending down with the glottis open may allow regurgitation of gastric content into the œsophagus. If there is straining, on the other hand, as at stool, pain may not occur, as the œsophagus may be effectively closed by forced contraction of the diaphragm. One of my patients told me "my stomach is in my chest, doctor", but she was not unduly concerned about it; but another said "it's murder getting my shoes on". The pain may be widespread, radiating through to the back, upwards into the shoulders and neck, rising to the angle of the jaw and into the hard palate. Pain may extend down one or both arms. On going to bed the patient may complain of discomfort or pain at once, or there may just be a feeling of sickness on lying down or a sense of bubbling in the chest, particularly when lying on the right side. In some, however, excruciating pain may develop. The patient may wake up during the night, about two o'clock, particularly after a late meal, with retrosternal pain which may be choking and unbearable and he may find himself bringing up acid fluid. The pain may be eased by alkalis and by getting up, standing and arching the back, and may be prevented by raising the shoulders on pillows or by blocking the head of the bed.

Other symptoms are related to food. A feature of the para-œsophageal hernia is lower retrosternal pain coming on at the beginning of meals eased by the patient getting up and walking round the room, after which he can continue his meal without discomfort provided he does not eat too much. In others, there may be a sense of discomfort or uneasiness coming on soon after meals lasting perhaps half an hour or longer, worse with big meals. One patient described it as something filling up and emptying slowly. Flatulence with belching is particularly common. If œsophagitis is present there may be a sense of rawness of the gullet with a burning or smarting pain at first on eating hard foods or hot, salty or alcoholic fluids. Difficulty in swallowing ensues and there may be regurgitation or vomiting. In some, only milk can be taken with any comfort. The pain may be relieved by alkalis but may return some time after meals, particularly if the patient is sitting down. These symptoms are often intermittent and there may be periods of freedom for days or even weeks, and nervous or emotional factors may be recognized as precipitating causes. There are other special clinical syndromes which may be due to hiatus hernia. Iron deficiency anæmia with chronic blood loss, positive occult blood in the stools may prove to be associated with a hiatus hernia. Frank hæmatemesis may occasionally occur, without an ulcer being demonstrated in conjunction with the hernia; it may be the cause of hæmorrhage, recurrent over intervals of months or years. Hæmatemesis occurring during pregnancy is likely to be due to hiatus hernia. Coronary thrombosis may be simulated by attacks of extremely severe retrosternal pain radiating to the neck and down the arm and perhaps lasting some hours. These may have a mechanical explanation and may sometimes be due to spasm of the diaphragm. Attacks of asthma may occasionally be induced by a hernia and it may cause a troublesome cough.

There are a number of difficulties arising in the diagnosis of a hiatus hernia. The symptoms of which the patient is complaining are not necessarily due to the hernia, but may be due to associated lesions such as peptic ulcer, cholelithiasis or diverticulitis. Of greater importance, however, is the fact that

the symptoms may be due to a neoplasm within the abdomen. For example, a pelvic carcinoma may masquerade with symptoms of flatulence and the discovery of a hiatus hernia may be very misleading. The only case of hiatus hernia in which cough was a major feature which I have seen, eventually turned out to have a bronchial carcinoma. The presence of peptic œsophagitis may cause diagnostic difficulties as it may simulate both cardiospasm and carcinoma of the œsophagus.

In our experience it may be more difficult to demonstrate the hernia on one occasion than another, or it may be shown only by bending the patient and not by tilting him on an X-ray table. In some patients with a typical history, it may not be possible to demonstrate the lesion.

What is the exact relation of incompetence of the cardia to hiatus hernia? Can it occur without hernia subsequently developing? What is the relation of such reflux to the development of œsophagitis? Reflux is commonly found without œsophagitis. I suspect that an increased basal interdigestive secretion such as occurs with duodenal ulcer may be a necessary concomitant. What is the true incidence of associated intra-abdominal disease, e.g. gall-stones, diverticulosis, and do they contribute to the pathogenesis of œsophagitis by causing increased gastric secretion or reflex shortening of the œsophagus? There is still much to be learnt about this condition.

Treatment

There is no doubt that the diagnosis which makes common sense to the patient and which explains his symptoms is, in itself, of great therapeutic value. The diagnosis of neurosis is dangerously easy to make, particularly in those middle-aged menopausal women with very widespread pain or discomfort, rising from the chest into the face and neck. In my experience the majority of patients can be adequately controlled with simple medical measures, and the question of surgery does not arise. Avoidance of stooping is often no great hardship and simple measures can be taken to overcome the need for doing so. Sleeping with the shoulders raised on pillows or by blocking the head of the bed is advisable and may give considerable relief. A bland reducing diet with small meals is desirable and certainly no late meals should be allowed. A simple alkaline mixture containing sodium bicarbonate is advisable before going to bed and after meals if there is discomfort. If there is evidence of œsophagitis, a strict basic ulcer régime with two-hourly milk feeds or semi-fluid feeds is required with special hospital care to prevent regurgitation. A tablespoonful of olive oil before meals and an antacid after each feed should be given. In some patients the question of surgical treatment will arise, but with frail, elderly patients it may be better to encourage the patient to remain on a restricted rêgime rather than undertake major operation. In a proportion of cases, however, I doubt if it will prove more than 5 to 10%, surgical treatment will convert a patient greatly crippled by this malady into a happy and comfortable member of the community.

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Mr. N. R. Barrett: "Hiatus hernia" is a pathological condition whose significance, symptoms, and special problems have only been appreciated recently. I propose to define the manner in which I shall use a number of terms connected therewith.

To me the *œsophagus* is that part of the alimentary canal, situated distal to the crico-pharyngeal sphincter, which is lined by squamous epithelium. There is no certain way of distinguishing between œsophagus and stomach except by identifying the squamous epithelium which lines the former as opposed to the columnar cells which make up the mucosa of the latter (Fig. 1). It is true that the relative shapes and sizes of the two viscera are different, and that the stomach is covered by peritoneum, but neither of these distinctions is valid.

I use the word "*gullet*" to define that part of the alimentary canal which traverses the mediastinum. Normally the gullet is formed by the œsophagus, but in abnormal circumstances part of the stomach may be included.

If a patient is born with a congenital short œsophagus the upper part of the gullet which traverses the mediastinum from the pharynx to the abdomen consists of œsophagus and the lower part is a tube of stomach. If the gullet of such a patient be examined by barium swallow, or anatomical dissection, it would be difficult to be sure where the œsophagus ended and the stomach began; in fact there are no clinical ways of determining this point, and it can only be settled by the endoscopist who can remove fragments of mucosa for biopsy. Two other points are relevant, namely, that in sliding hiatal hernia and in congenital short œsophagus a pouch of stomach lies in the mediastinum and the greater part of this pouch is not covered by peritoneum; it is an extension upwards of the normal bare area of the stomach. Secondly, in cases of sliding hiatal hernia and congenital short œsophagus the mediastinal stomach is to all external appearances identical with the œsophagus; it does not look like a stomach which has been simply moved to a new place, and in this respect it is importantly different from the herniated stomach in other varieties of diaphragmatic hernia.

The *cardia* is the point where the squamous mucosa of the œsophagus joins the gastric mucosa.

Normally this lies immediately below the diaphragm and corresponds with the level of a "sphincter mechanism" which prevents reflux of gastric juice into the œsophagus. But the site of the "sphincter" and the boundary between the two mucous membranes may be separated and hence the "cardia" and the "sphincter mechanism" are not synonymous. Moreover, when a pouch of stomach has slid into the mediastinum the mucous membrane which lines that pouch is not *ectopic gastric mucosa* because it is in direct continuity with the lining of the stomach. True ectopic gastric islets can be found in most normal œsophagi but the islets lie in the post-cricoid region and not at the bottom.

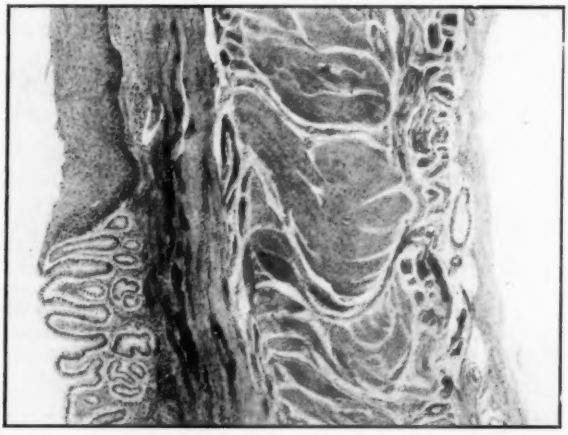

FIG. 1.—This is a drawing showing the histological appearances of the œsophagus and the stomach at the level of the cardia. Apart from the mucous membranes there is no difference in the histology of the œsophagus and of the stomach.

A "*hiatus hernia*" is a hernia through the œsophageal hiatus of the diaphragm and Sir Astley Cooper was the first to stress that herniæ through this hiatus are acquired and not congenital; and thus it follows that practically all cases at present described as examples of "congenital short œsophagus", are, in truth, acquired abnormalities. This applies to infants as well as to older patients. There are three main varieties of hiatal hernia.

(1) In *sliding hiatal hernia* (Fig. 4) a part of the stomach passes up into the posterior mediastinum "en glissade", and forms the lower reach of the gullet. Being "en glissade" the sac is empty, insignificant and not concerned with the effects, symptoms or treatment; strangulation need not be considered. Sliding hiatal hernia is unique in its anatomy, because the œsophagus is the only part of the gut (apart from the rectum) which passes through a "foramen"—namely the hiatus in the right crus of the diaphragm—and the term hernia here describes a slide upwards of the whole gut in such a way that the part which was immediately below the hiatus comes to lie above it. The hernia is not comparable to prolapse of the rectum because there is no intussusception—merely a slide of the whole gut.

Sliding hiatal hernia can affect any person from birth to old age. It is a common abnormality which seldom reaches a large size, and the symptoms it produces are referable to the fact that the "sphincter mechanism", between the stomach and the œsophagus, has become incompetent. This allows regurgitation of digestive juices, and the œsophagus is generally unprotected against secretions from the stomach or the duodenum; on the other hand every gullet is not equally sensitive to these juices and reflux is not certainly harmful. In general the mucous membrane of the œsophagus becomes inflamed, so that it bleeds easily and patches of desquamation and leucoplakia form. This may persist, subside, or recur for years, but it can progress through the musculature of the œsophagus and involve the surrounding lymphatics, glands and mediastinal tissues. The "sliding" hernia then becomes fixed and irreducible.

Prolonged mural fibrosis leads to the formation of stricture and although at first this is generally a ring, as time passes, and particularly in infants, it spreads and mounts up in the wall of the œsophagus (ascending œsophageal fibrosis) and may eventually be several inches in length.

This sequence of changes was clearly put together by Allison; I refer to it as "reflux œsophagitis".

The signs and symptoms of a sliding hiatal hernia are principally those of "reflux œsophagitis" and it is this latter condition which dominates the pathology and the treatment. The hernia, *per se*, is immaterial.

Congenital short œsophagus (Figs. 2 and 3) is included by some as a variety of sliding hiatal hernia, This is absolutely unsound, and, if acted upon, leads to disaster in treatment. Congenital short

œsophagus is a specific entity; a true but rare congenital abnormality. The condition is one in which the "cardia" has always been situated above the diaphragm and the œsophagus cannot be lengthened surgically. The difference between this congenital deformity and sliding hiatal hernia is that in the latter the "cardia" can be replaced below the diaphragm unless secondary inflammatory factors have supervened and fixed the tissues by scar.

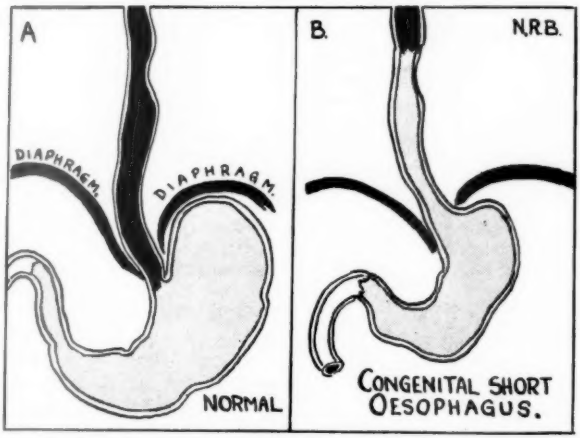

FIG. 2.—The œsophageal squamous mucosa is black and the gastric mucosa is stippled.
A.—In the normal individual the stomach and the œsophagus are different not only in external appearances but also in regard to the epithelium which lines them.
In B, which depicts a congenital short œsophagus, part of the gullet is composed of stomach. To all external appearances this "mediastinal stomach" simulates œsophagus but it is lined by columnar epithelium.

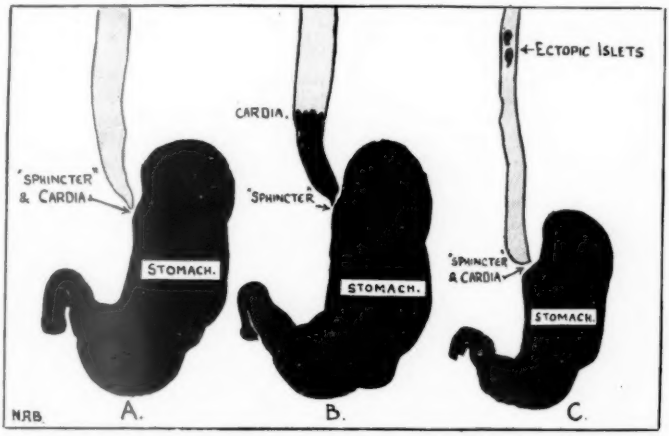

FIG. 3.—This figure shows the œsophageal mucosa (stippled) and the gastric mucosa (black).
A.—Normally the level of the "sphincter mechanism" and the cardia are identical.
B.—Shows that, in a patient whose barium swallow X-rays are apparently normal, the cardia and the "sphincter mechanism" do not correspond. Such a patient has gastric epithelium above the "sphincter". Such epithelium would be wrongly described as "ectopic".
C.—Ectopic gastric islets do occur in the œsophagus but are situated at the upper end.

The reasons that a congenital short œsophagus cannot be elongated are not only that it extends over its natural span, but that it is anchored by its blood vessels to the reach it already occupies. By contrast a "sliding hiatal hernia" carries its blood vessels with it as it slides up into the mediastinum and the parts can be replaced in their normal positions.

(2) A *para-œsophageal hernia* (Fig. 5) is different for two reasons. First, the gut lies inside a sac

and the lesion is comparable to a Richter's hernia, and secondly, the "sphincter mechanism" and the "cardia" remain in their normal positions relative to each other and hence there is no "reflux œsophagitis". The sac contains the greater curve of the stomach together with the omentum attached to it, which results in those parts of the stomach, which are in the sac, being upside down. The reason for this is that the lesser curve is stretched, immobile, between two fixed points—the œsophageal hiatus and the pylorus, and the greater curve is sucked up into the sac. The neck of the sac is generally wide, adhesions and loculations are rare, and it is unusual for any viscus except the stomach, or rarely the colon, to be concerned. Strangulation is possible but unusual.

A para-œsophageal hernia may be of any size and in infants it may contain the whole stomach. It is harmful because it is a space-occupying lesion in the posterior mediastinum lying immediately behind the heart, and because part of the stomach, which has capsized, is not only prone to abnormalities such as peptic ulceration, but when distended with gas produces discomfort, flatulence and eructations

Both sliding hiatal hernia and para-œsophageal hiatal hernia can act as the trigger mechanism for attacks of angina pectoris

(3) A *mixed hiatal hernia* (Fig. 6) is the rarest of the three types and is found more often in infants than in older persons. It consists of a combination of the first two. The patient develops a sliding hiatal hernia, and a para-œsophageal bulge is added to it. The "sphincter mechanism" is often ineffective, and, in consequence, the symptoms are a mixture of those of the first two types.

The "Sphincter Mechanism"

By far the commonest hiatal hernia is the sliding variety and if we are to treat this either expectantly, medically, or surgically we must know about the so-called "cardiac sphincter".

It is certain that in normal subjects a mechanism exists which prevents reflux. Temporary incompetence of this mechanism produces "heartburn" and persistent reflux, "œsophagitis". The nature of this barrier to reflux is not certainly known, but some facts which have a bearing upon it are available.

No muscular sphincter, in the accepted anatomical or physiological senses, is demonstrable. Nor does the key lie in some form of contraction of the circular fibres of the lower œsophagus, because the basis of Heller's operation for achalasia is to divide these fibres and the particular merit of the procedure is that it is not followed by reflux.

Reflux does not occur normally, but vomiting, rumination and regurgitation of gas from the stomach are possible and at least partially controllable. Indeed circus entertainers such as the "Human Ostrich" can swallow rats into their stomachs and regurgitate them alive. Thus the mechanism functions naturally, like respiration, but can be voluntarily controlled after practice.

It has been said that control is effected because the junction between the stomach and the œsophagus is normally situated in the "liver tunnel", and, when the fundus distends, the bulge compresses the lower part of the gullet against the liver. But the "sphincter" can function normally away from the "liver tunnel". For example the operation for curing sliding hiatal hernia, in which the gullet is purposely brought through a new and artificial orifice in the dome of the diaphragm, is not complicated by pathological reflux.

Another suggestion is that the right crus of the diaphragm acts as a sling which obstructs the gullet when the diaphragm contracts. This is the so-called "diaphragmatic pinchcock". There is no doubt that the act of *swallowing* can be obstructed temporarily by deep inspiration and that this obstruction is due to the pull of the crural sling which indents the left margin of the gullet. This "sphincter" is above the normal cardia and can be palpated at laparotomy by passing a finger into the stomach and thence into the lower œsophagus. But there is no evidence that it prevents *regurgitation*. At best such a mechanism could only work intermittently, that is, at the end of each inspiration, leaving the fairway open for most of the time. It might be argued that the pinchcock works at the culmination of inspiration because at that time the intra-abdominal pressure is most raised and reflux might be encouraged on this account. But I believe that the crural sling is not concerned with preventing reflux in any way because diaphragmatic paralysis does not lead to incompetence, and because reflux does not occur in the presence of total eventration of the diaphragm.

Taking these points into consideration, I submit that the competence of the "sphincter" does not depend upon any extrinsic mechanism such as the diaphragmatic pinchcock, nor is it concerned, as many believe, with the circular muscle fibres of the lower œsophagus. *The mechanism which prevents reflux from the stomach is wholly within the stomach* itself, and there are two points which, in my opinion, support this theory.

If the œsophagus and the stomach, removed from a patient at autopsy, are laid out in such a way that the gullet enters the junction of the greater and lesser curves at an acute angle, then liquid injected at the pylorus will be held by the cardiac incisura. But if the gut is stretched out so that the œsophagus enters the stomach like the handle of a bell, liquid injected at the pylorus passes into the œsophagus without obstruction. Thus if the acute angle between the greater curve and the terminal œsophagus (i.e. the cardiac incisura) can be maintained and controlled, a "sphincter" will be present.

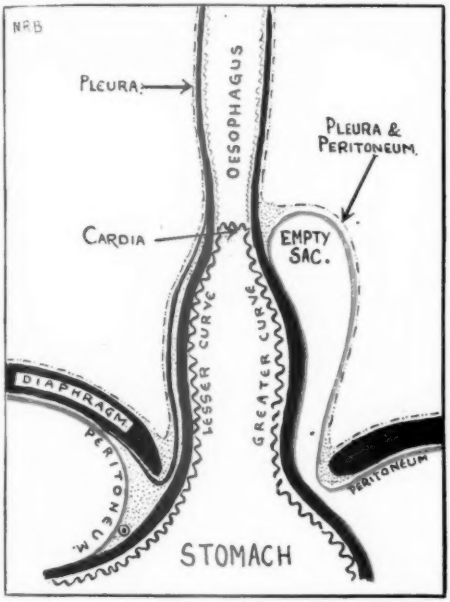

FIG. 4.—Sliding hiatal hernia. Diagram to show the manner in which the fundus of the stomach slides up into the mediastinum "en glissade".

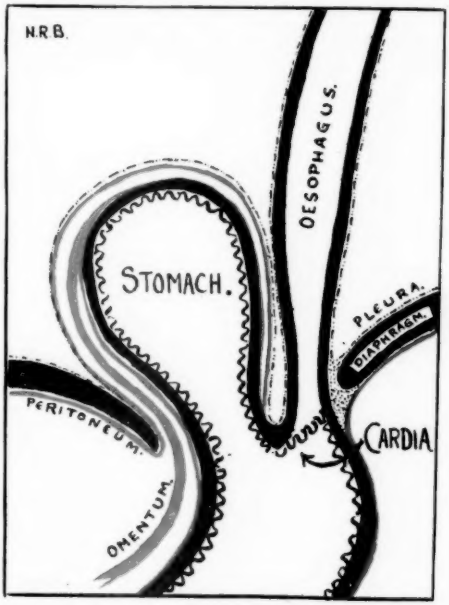

FIG. 5.—Para-œsophageal hernia. In this diagram the greater curvature of the stomach has passed up into a peritoneal sac which lies in the mediastinum. The cardia is in its normal place, below the diaphragm, and the "sphincter mechanism" functions normally.

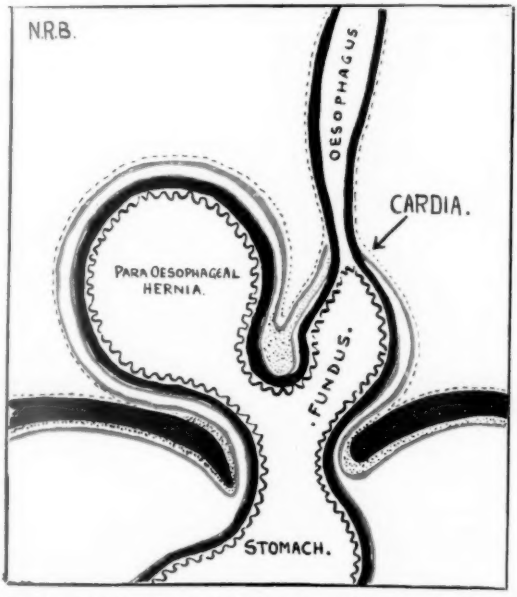

FIG. 6.—A mixed hiatal hernia. In this diagram the lesion depicted is a combination of the first two varieties.

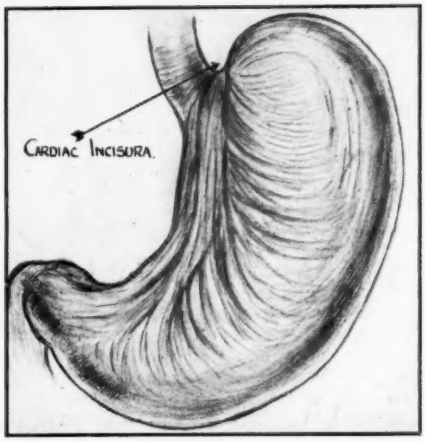

FIG. 7A.—This is a drawing made from a freshly dissected human stomach. *Note.*—The stomach was first turned inside out, and the mucosa was then removed. The muscle fibres shown are those situated immediately deep to the mucous membrane. The purpose of the dissection is to demonstrate the fibres which encircle the cardiac incisura and which could act as a sling as described in the text.

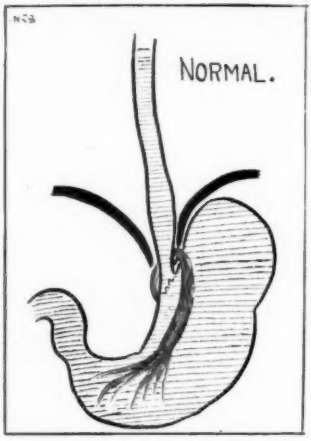

FIG. 7B.—Diagram to illustrate the manner in which the muscle sling shown in Fig. 7A could act as a sphincter to prevent reflux of gastric secretion into the œsophagus.

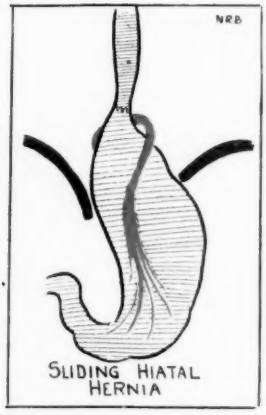

FIG. 8.—In sliding hiatal hernia the sphincter is incompetent because the gastric sling can no longer control the cardiac incisura.

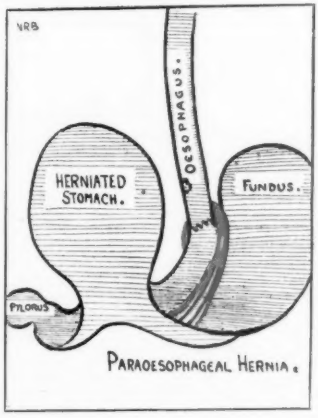

FIG. 9.—In para-œsophageal hernia the gastric sling is not disturbed and, in consequence, reflux from the stomach does not occur.

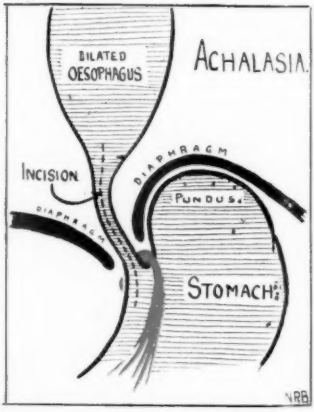

FIG. 10.—Surgeons have for long been puzzled as to why the "sphincter mechanism" remains competent after Heller's operation. The author submits that the explanation lies in the fact that the incision made through the muscle fibres of the lower œsophagus does not impinge upon the gastric sling, and so does not impair its efficiency.

There are muscle bands beneath the mucosa of the stomach, which could function in this way. They course up the posterior surface of the viscus, encircle the cardiac incisura and double back across the anterior surface of the stomach (Figs. 7, 8, 9, 10). These fibres form a sling which, if it comes into action, pulls down the cardiac incisura and obliterates the fairway. This sling could only be effective if the parts are normally disposed to each other. Hence the reflux which complicates sliding hiatal hernia and is absent in the para-œsophageal variety. Hence the efficacy of Heller's operation, and the failure of cardioplasty or œsophagogastrostomy.

The Cause and Mechanism of Sliding Hiatal Hernia

It is worth enquiring into the cause of sliding hiatal hernia because to understand the cause will facilitate treatment.

I now reject the theory that the œsophagogastric junction is drawn up into the mediastinum by active contractions of the longitudinal muscle fibres of the œsophagus. The most that the longitudinal muscle probably does is to take up the slack as the pouch of stomach ascends.

I no longer believe that the stomach is dragged up into the mediastinum by contraction of scar tissue secondary to "reflux œsophagitis". There are two reasons which deny this possibility: The first, that fibrous stricture of the œsophagus, occurring in the same place but due to other causes, such as the swallowing of a corrosive, does not drag up a pouch of stomach as the scar matures; and the second, that operations have shown that the cardia lies in the mediastinum before inflammation has transgressed the muscular coats of the œsophagus. On the other hand, once the inflammatory process has become established in the musculature of the gullet, the upper limit of the stricture mounts in the mediastinum—a fact which has often been proved by serial X-ray examinations.

Another important aspect of this topic is the exact part which the œsophageal hiatus plays in the ætiology of hiatal hernia. It is manifest that a hernia through the diaphragm only occurs through a hole in the diaphragm—or conversely, no hole, no hernia. The œsophageal hiatus is a hole, and one whose margins are not intimately applied to the wall of the gullet. But I can see no easy answer to the following questions. Why is hiatal hernia almost entirely confined to the fundus, or the greater curvature of the stomach? Which comes first—a lax hiatus which permits a hernia, or a hernia which distends and distorts a normal hiatus? Whatever be the answer to these queries I deduce two points; first that the œsophageal hiatus itself is concerned with the development of all types of hiatal hernia; and secondly that this statement does not bear in any way upon the proposition I have already made that the œsophageal hiatus (diaphragmatic pinchcock) is not concerned with the "sphincter mechanism" of the stomach.

Hiatus hernia occurs as a result of a combination of circumstances. These include the thrust upwards from below, exerted by the muscles of the body wall (transversus abdominis, levator ani and the diaphragm) whose primitive function it is to compress the cœlom; or by any physiological or pathological process which raises the intracœlomic pressure. To these forces is added the suction upwards exerted by the relatively negative intrathoracic pressure. That the negative intrathoracic pressure is transmitted to the mediastinum is demonstrated by paradoxical œsophageal respiration.

It has always seemed to me more difficult to explain why a sliding hiatal hernia does not occur in all people rather than to account for its appearance in some. What, in fact, normally holds the parts in their accustomed anatomical site?

The œsophagus is not closely applied to the margins of the hiatus: indeed the degree of normal. slide, up or down, is considerable and varies from subject to subject. It is at its most in infants and old persons. If you study this point of mobility superficially in the autopsy room you may come to the conclusion that the principal tether is the two vagi; but in life these nerves play no part because they are not fused with the wall of the gullet unless, or until, they become engulfed in penetrating inflammation and scar. It has been customary to lay stress also on the phreno-œsophageal ligaments as the principal anchors. These ligaments are tenuous bands of tissue fixed at one end to the undersurface of the diaphragm and at the other to the lower segment of the œsophagus. I believe that they play no part in preventing the development of hiatal hernia in infants, and a negligible part in adults. The point is taken because operations designed to cure sliding hiatal hernia by plication of these filaments of tissue have not in my experience succeeded.

I believe that the key to this question lies in the anatomy of the left gastric artery. It was Moynihan who first emphasized that this vessel binds the upper end of the lesser curve of the stomach to the posterior abdominal wall. Normally the left gastric artery approaches the stomach at the apex of the bare area; it ends by dividing close to the wall of the stomach into two branches one of which tracks up to supply the lower œsophagus and the other courses down along the lesser curve. These arteries are applied to the wall of the gut by their short branches which enter the œsophagus and the stomach at right angles and thus anchor the whole region to the cœliac axis.

If the mesentery of the left gastric artery is long, or if its terminal branches lie at some distance from the edge of the lesser curve of the stomach, a sliding hiatal hernia can occur. Such a hernia is only limited in its upward slide by the length of these blood vessels.

If on the other hand, the left gastric artery is short, or inextensible, as it may be if it is atheromatous,

the top of the lesser curve is pinned down and no hernia can occur unless the hiatus is unduly patulous, in which case the greater curve moves up into the sac, and a para-œsophageal hernia is the result.

Principles of Surgical Treatment

In the surgical management of *sliding hiatal hernia* two distinct objects must be achieved:

First the hernia must be reduced and the parts fixed in such a way that the hernia does not recur.

Secondly the operation must leave the patient with a competent sphincter. To do this I postulate that the fundamental necessity is to leave the region of the cardiac incisura so placed, and so freed, that the gastric sling which I have described can allow the flow of food from the gullet to the stomach and yet prevent reflux of gastric secretions upwards.

The surgical problem in *para-œsophageal hernia* is different, because here the prime necessity is to reduce the hernia and prevent recurrence: that is, "œsophagitis" is not vital.

If a stricture has developed as well as a hernia, the problem is much more complicated. The first essential is now to overcome dysphagia, which can be so severe as to threaten life. Dilatation of the stricture, or excision with anastomosis of the stomach to the œsophagus, results in a permanent hernia and reflux œsophagitis which inevitably proceeds to further stricture. Both these methods are contra-indicated. The stricture should only be dilated *after* the gastric secretions have been reduced by vagotomy or subtotal gastrectomy. The late results of these methods are doubtful but early successes have been claimed. The only certain way of overcoming the stricture and curing the hernia is to excise the stricture, close the stomach, replace the stomach in the abdomen, and anastomose the proximal end of the œsophagus to the jejunum. This is œsophago-jejunostomy; it solves the problems of stricture and reflux, but the effects it may have upon metabolism are not yet certain.

The Cause of the Symptoms

I conclude on a note of doubt. I do not know why a hernia through the œsophageal hiatus causes all the different symptoms it does. The severity of these bears little relationship to the size of the hernia and they are unlike those caused by hernia elsewhere; severe pains can be present without endoscopic evidence of acute œsophagitis; acute œsophagitis may upon occasion be symptomless. These points, and others, must be fitted in to any theory which is said to explain the signs and symptoms of hiatal hernia.

Professor A. S. Johnstone: *The Radiology of Hiatus Hernia*

My remarks will be confined to the sliding type of gastric hernia which is by far the commonest, and, in its early stages, the most difficult to recognize. Great responsibility now rests upon radiologists for their clinical colleagues expect them to produce this abnormality on every occasion when other investigations appear to exclude such lesions as coronary thrombosis, cholecystitis or gastric ulcer. The incidence of hiatus hernia is high, much higher in the West Riding than is generally appreciated for in a recent series by Pickard (1952), it was found in approximately 11% of all barium meals and was commoner than gastric ulcer. Bearing this in mind one might expect a high proportion of positive findings in the type of case just mentioned. It is very necessary, however, to guard against over-enthusiasm for there is much confusion and misinterpretation of radiological appearances the causes of which I shall discuss. Our difficulties would be lightened if we studied the physiological rather than the anatomical aspects of hiatus hernia.

The diagnosis of this hernia is, at present, based on anatomical features, namely, the recognition of part of the stomach protruding through the œsophageal hiatus of the diaphragm. When the gastric fundus or even part of the pyloric antrum lies within the thorax the diagnosis is readily made. On the other hand the early case appears as a small dilatation, only slightly wider than the œsophagus, lying immediately above the hiatus. The œsophagus joins the dilatation at its apex and appears slightly constricted for a centimetre or so above the junction. Stress must be laid on the œsophageal entry into the dilatation for if it is eccentric then the picture is pathognomonic of gastric herniation.

Any small projection to the left side, seen immediately above the diaphragm, should be considered a hernia, especially if the greater curvature of the stomach, just above the cardia, presents a concave border when examined erect. Otherwise the diagnosis must depend on the examination of the mucosa. Œsophageal mucosa is represented by three or four fine longitudinal lines, whereas gastric folds are thicker and coarser. Sometimes they may run transversely, or branch or present a varicose appearance; each feature being characteristic of mucosa lying along the greater curvature. The mucosal junction may at times be clearly defined but more often the change is imperceptible.

These criteria—namely a pouch and gastric mucosa—for the recognition of a gastric hernia would seem acceptable and should present little difficulty but unfortunately the problem is not so readily solved. For over a hundred years anatomists have argued that the œsophagus is not a simple tube of uniform calibre but may have either one or two dilatations—or pouches—at the lower end. Arnold (1838) described one in the last 3 cm. which he termed the "vor Magen". Subsequently it became known as the cardiac antrum. Some twenty years later Luschka (1857) found in addition to Arnold's pouch

another variation in which there were two pouches. The second one lay above the diaphragm and he called it the "vor Magen": later it was renamed the "phrenic ampulla". These observations were based on post-mortem studies.

In radiological studies of the living it has been possible to demonstrate that the infra-diaphragmatic portion of the œsophagus is in most cases non-existent and the œsophagus and stomach fuse at the lower margin of the hiatus. Further one can frequently show the mucosal change taking place in the terminal segment of what we still call anatomically the œsophagus, although Barrett has put forward a strong claim for the stomach (Fig. 1). This junction may be occasionally recognized as a ring or the folds may thicken gradually. It is well known, however, that the junction is irregular and there may be one or two centimetres difference between its level on the opposing walls (Fig. 2). These observations were proved by the application of silver clips at points selected for biopsy. It has been frequently stated that the mucosa in the lower end of the œsophagus is very mobile and under certain conditions, such as belching, may project into the œsophagus. The only case we have checked did not bear out this hypothesis. After attaching a clip to the mucosal junction radiographs were taken before and during a belch. These films showed that the clip remained stationary while the diaphragm descended appreciably producing the illusion that the clip had moved upwards.

FIG. 1.—Drawing to illustrate the author's conception of gastric mucosa lining the terminal portion of the œsophagus or the cardiac antrum.

FIG. 2.—Point J marks the site where radiologically the mucosal junction was located. The clip (C) is seen to lie about 2 cm. distal to this point.

It is always possible to demonstrate radiologically a pouch corresponding to the anatomist's phrenic ampulla if the diaphragm is held in sustained contraction while barium is swallowed. The hiatal canal is demarcated by a band 1·5–2 cm. wide which constricts the œsophagus. As the peristaltic ring travels down the œsophagus pushing the bolus before it a pouch develops in the segment immediately above the diaphragm. The dilatation increases until the pressure within it equals the force of the wave. Then, after a momentary pause, the ring relaxes and barium flows back towards the upper end. The pouch collapses but not always completely for it may leave another small dilatation which is thought to be related to the insertion of the phreno-œsophageal sheath. Sometimes the phrenic ampulla has two lateral notches which are said to be characteristic features. Should the gastric mucosa extend partly into this pouch it would resemble a hernia.

Another source of confusion may arise if the central tendon is weak and bulges under stress in the manner of the abdominal wall in a direct inguinal hernia. Should the stomach lie adjacent to the tendon it may bulge out into the thorax during inspiration mimicking a sliding hernia.

I do not wish to pursue in detail the technical aspect of the examination but it has always been the rule in the General Infirmary at Leeds to examine every patient undergoing a barium meal in both erect and horizontal positions. In addition, special attention has been paid to the production of a hernia if it could be done by physical methods which included abdominal compression during inspiration and expiration. Other measures such as straining and coughing were also used. As stated earlier it is easy to produce a pouch or dilatation above the hiatus and we relied upon the presence or absence

of gastric mucosa as judged radiologically to make a diagnosis. The method seemed to work satisfactorily until in the course of one week we came across two cases in which our radiological findings were not confirmed by œsophagoscopy. In each case clips were applied to the mucosal junction and the levels were found to be different from those we had thought to be established on the films (Fig. 3).

It therefore became clear that a diagnosis based on anatomical criteria might be erroneous and our attention was turned to the physiology of the cardia. Its main function lies in the prevention of regurgitation particularly under conditions of sudden strain. Jackson (1929) considered that the pinch-cock action of the diaphragm, due largely to the splitting of the right crus, played the most important part in this intricate mechanism. Some credit was given to the cardiac sphincter, the existence of which has long been a matter of discussion and conjecture. While there is no true sphincter in the anatomical sense there is a muscular arrangement, with a similar function. This can be readily demonstrated by observing a small column of barium which may remain in the œsophagus for an appreciable time, quite unaffected by diaphragmatic movement. The barium quickly passes into the stomach after swallowing. Dick and Hurst (1942) contended that the obliquity of the cardia produced a valvular effect which contributed to its efficiency. There is no doubt that in the para-œsophageal type of hernia this mechanism is often preserved and regurgitation into the œsophagus is not nearly so free. As Hurst had laid so much stress on the deleterious effect of gastric juices on the œsophageal mucosa, it seemed that more attention should be paid to regurgitation and less to the presence of a gastric pouch,

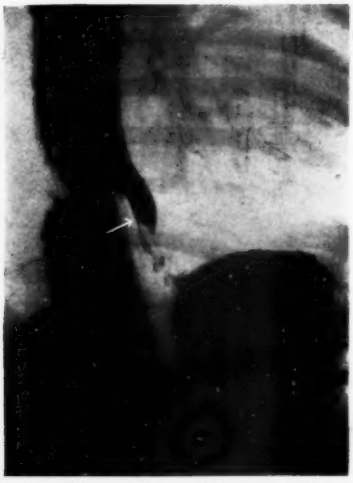

FIG. 3.—Clips have been placed on the junction of squamous and columnar mucous membrane. The clip on the posterior wall (indicated by an arrow) is higher than that on the anterior. In this case both clips are above the diaphragm.

FIG. 4.—Regurgitation occurring into œsophagus associated with small hiatus hernia.

(Figs. 1–4 are reproduced by kind permission of the Editor, *Journal of the Faculty of Radiologists*, 1951, 3, pp. 59, 61 and 62, The diagnosis of early gastric herniation at the œsophageal hiatus, by A. S. Johnstone.)

which hitherto had been the mainstay of our diagnosis. Once the protective mechanism at the hiatus becomes incompetent the radiological picture is chacteristic, for barium can be made to flow back into the œsophagus, often with considerable ease, and frequently it occurs with only slight straining or even on normal respiration (Fig. 4).

It is not necessary in every case to have a gastric hernia, for reflux without herniation is occasionally found. Certain hypothetical explanations such as relaxed cardia and hiatal insufficiency have been put forward. It is assumed that the anchorage of the stomach is secure and there is no hernia. On the other hand one has to consider another type of hiatus hernia in which the change from œsophageal to gastric mucosa takes place at a much higher level in the œsophagus. In these cases there may be no dilatation to suggest the hernia. These cases are described by Barrett as true congenital short œsophagus.

The majority of patients who show free reflux have œsophagitis or deep ulceration. Our figure is over 70% and it is evident that the squamous mucosa cannot withstand prolonged and frequent bathing with gastric juices. It therefore seemed reasonable to assume that in almost every case which showed reflux from the stomach œsophagitis would be found. The radiological diagnosis of œsophagitis

is often equivocal and the lesion can only be excluded by œsophagoscopy. On analysis of clinical histories many of our patients complained of retrosternal pain brought on by bending or lying on the right side. We therefore included bending in the technique of our examination and were able to display the free return of barium into the œsophagus on deep breathing or straining. It was not found, however, that this method had any advantage over the routine examination in the supine position.

Some time later new observations began to disturb our confidence. In 2 cases with classical histories of peptic œsophagitis neither hernia nor reflux could be obtained. The patients were asked to belch and while making the effort they produced a hernia through the hiatus and regurgitation took place. In other patients we noted that the effort of swallowing appeared to open the cardia and allow the return of gastric contents although only a minimal hernia could be found. In yet another in whom there was no hernia free regurgitation occurred each time on belching. In a somewhat different case of a true ruminator the patient was able to control his hernia. It was found quite impossible to demonstrate the hernia if the patient did not allow his diaphragm to relax. The moment he was willing to co-operate, he made a retching movement and the hernia appeared, followed by gastric contents which returned freely into his mouth. In this case, however, there was no evidence of peptic erosion. It appears from the examples just quoted that there may be some trigger mechanism which allows herniation. It is obvious that if this is so we do not understand it, but I am becoming more convinced that swallowing plays an important part. It is possible that the elevation of the pharynx exerts a pull on the cardia preparing it to relax, and at the same time may exert some influence on the hiatal canal.

It is also becoming evident that the significance of reflux or regurgitation into the œsophagus is difficult to evaluate. There appears to be no doubt that it is abnormal, and, although no figures are available, we do not expect to find it in the average healthy individual. The late results of operation have not yet been published by Allison but his cases are being examined. The large majority are surgically cured and relieved of their symptoms. There are some in whom recurrence has taken place and it is extremely interesting to note that many are clinically well, although the physiological breakdown is still present.

And so, having tried to build up a theory that gastric reflux into the œsophagus is responsible for most of the ills connected with hiatus hernia, it must be admitted that the foundations are somewhat shaky, for we cannot explain why reflux takes place in some individuals who have no sign of hernia; why the flow into the œsophagus may be dependent on physiological actions such as swallowing; why a hernia may be readily demonstrated at one examination but not at another; why a classical case of rumination had no œsophagitis; and why operation, even if a physiological failure, seems to cure the patient.

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Mr. **R. H. Franklin**: *Hiatus Hernia in the Adult*

Most of the patients fall into one of three groups:—Those in whom a cone of stomach is drawn up into the chest and as a result superficial ulceration of the œsophagus occurs. The resultant œsophagitis may produce spasm or a fibrous stricture. In the second group the thoracic stomach is, itself, the seat of ulceration and this ulceration follows closely the course of an ulcer in the normally placed stomach and may produce severe hæmorrhage. This type of case may be difficult to diagnose because the thoracic stomach may resemble the œsophagus in naked-eye appearances, and in more than one of my patients in whom a narrowed ulcerated length of œsophagus extended up to the arch of the aorta, subsequent histological examination showed that what appeared to be œsophagus was lined by gastric mucosa throughout its entire length. A third type consists of what is essentially a para-œsophageal hernia associated with a very small hiatal hernia.

The variation in the anatomical arrangements makes it difficult to treat all the cases by the same method. A medical régime should be employed in the first instance and this régime is exactly the same as would be carried out for a duodenal ulcer, with the addition that regurgitation from the stomach is discouraged by suitable posture. Medical treatment is unlikely to help those patients in whom a stricture has formed or in whom there is a chronic gastric ulcer in the thoracic stomach. In these patients surgery will be required. In the case of an extensive stricture and ulceration of the stomach, resection of the affected portion of the œsophagus may be necessary.

A group of 8 patients who failed to respond to medical management and who suffered from small hiatal herniæ with œsophagitis were treated by carrying out a Billroth I partial gastrectomy below the diaphragm. Two of these patients had evidence of stricture before operation. Following the partial gastrectomy, 2 patients now express themselves as completely normal, a further 4 are very pleased with the result and the remaining 2 are improved. This method of treatment would appear to have a place in those patients who are not suitable for the more major abdomino-thoracic procedures, or in whom it may be impossible to improve the anatomical arrangements at the cardiac sphincter.

The operation may owe its success both to the diminution in the gastric acidity and to the fact that a Billroth I gastrectomy tends to prevent the stomach passing up into the chest. The method is not likely to be successful in those cases in which the thoracic stomach has itself become the seat of ulceration.

Mr. G. H. Wooler: *Mechanism of the Cardia*

Mr. Barrett has confused ideas of the mechanism at the cardia which, if they did occur, would produce reflux œsophagitis in most people. He relies solely on the oblique muscle fibres of the stomach to guard the cardia, and showed us a diagram with a thickened band of this muscle encircling the cardiac end of the stomach which he emphatically states is the only structure preventing reflux of gastric contents. However, above this muscular band there was gastric mucosa in direct communication with the œsophagus for the "band" was not shown to encircle the cardia but lay distal to it. I fully realize that at the present time hiatal hernia of the stomach is a fashionable surgical condition but if Mr. Barrett's theory is correct every person should have a small gastric pouch at the lower end of his œsophagus before the mechanism guarding the œsophagus from the stomach is encountered. The oblique muscle fibres of the stomach do play a minor part in the control at the cardia by increasing the angle between the œsophagus and the stomach; but the function of the diaphragm cannot be disregarded for four reasons:

(1) Anatomically thick muscle fibres coming mostly from the right crus of the diaphragm encircle the cardia like a sling as, in a similar way, the pubo-rectalis muscle encircles and controls the ano-rectal junction.

(2) Radiologically, barium is seen to be held up at the cardia during inspiration; but during expiration when the diaphragm relaxes, barium flows through the cardia into the stomach.

(3) At œsophagoscopy the pinchcock action of the diaphragm may be seen and felt as the instrument is passed through the cardia into the stomach.

(4) At operation if two fingers are placed in the œsophageal hiatus and then the phrenic nerve stimulated, the diaphragm contracts and the fingers are gripped by the muscle sling which Mr. Allison has described (1951, *Surg., Gynec. Obstet.*, **92,** 419).

Surely this is sufficient evidence to bring the diaphragm into the picture. In fact one cannot do without it when repairing a hernia. Perhaps Mr. Barrett treats all his cases medically?

Dr. W. A. Bourne: *Factors which Determine the Occurrence and Type of Hernia*

Differences between intra-luminal and intra-cavital pressures provide another factor in determining the occurrence and type of hernia. A thoracico-abdominal intra-cavital pressure difference is applied to the hiatus œsophageus. When the hiatus is lax and the cardia is incompetent, this difference may (another factor permitting) cause reflux of gastric contents and predispose to a sliding or short-œsophagus hernia. If the cardia is competent, reflux of acid, enzymic, or gaseous contents cannot occur, and the pressure difference is applied to the distended fundus, which lies against the hiatus. A para-œsophageal hernia then results. The two types of hernia are at this stage to some extent mutually exclusive. However, though the short œsophagus drags up the stomach in one type, and the aspirated fundus drags up the cardia in the other, if this latter process goes on far enough the cardia will escape from the hiatus and become incompetent.

The other factor referred to concerns intra-luminal pressure. In a number of cases which I have observed the intra-œsophageal pressure is negative—becoming more negative in inspiration, while, when observable, the intragastric pressure is positive—becoming more positive in inspiration. This must be a fallacious observation, since negative intra-œsophageal pressure and positive intra-gastric would make transit into the stomach difficult. (Intubation of the œsophagus probably tends to inhibition.) A further factor preventing regurgitation must be tone in the œsophageal wall, and when this is absent, as in sclerodermia, regurgitation occurs and "sliding" hernias become frequent.

I believe that the intrinsic mechanism controlling reflux at the cardia, postulated by Mr. Barrett, may be disturbed by neoplasm. In 3 cases in my experience, the rather sudden appearance of simple œsophagitis has been the presenting symptom of infra-cardiac gastric cancer, and the X-ray appearances were of "sliding" hernia, as in one photograph shown to the meeting.

Section of Neurology

President—Professor P. C. P. CLOAKE, M.D., F.R.C.P.

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The Pathology, Diagnosis and Treatment of Intracranial Saccular Aneurysms

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THIS paper is based on a study of 120 aneurysms which occurred in 114 patients observed at the Neurosurgical Clinic in Stockholm since 1932 (Table I).

TABLE I.—TOTAL NUMBER OF PATIENTS AND ANEURYSMS

	Patients	Aneurysms
Int. carotid artery	43	44
Infraclinoid	9	
Supraclinoid	34 (35)	
Bifurcation of int. car. art.	5	6
Proximal part of ant. cerebral art.	8	8
Ant. comm. art.	23	23
Distal part of ant. cerebral art.	5	6
Middle cerebral art.	24	24
Basilar and vertebral artery	3	3
Multiple aneurysms with different localization:—		
Int. car. art. and bifurcation	2	4
Int. car. art. and middle cer. art.	1	2
	114	120

In all cases except 5 the aneurysm was verified either at autopsy, at operation or by angiography. The 5 unverified aneurysms occurred in patients exhibiting the typical picture of ophthalmoplegia associated with migraine or subarachnoid hæmorrhage. 5 might have been of arteriosclerotic nature while all the rest were congenital. Forbus (1930) attributed the development of congenital aneurysms to the persistent pressure against the weak point of bifurcation of an artery, where the media of the arterial wall is defective. An alternative theory was advocated by Dandy (1944), who held that these aneurysms have their favourite sites and are not always located at the point of bifurcation. On the basis of a study of the embryonic development of the cerebral arterial tree by Dorcas Hager Padget, he considers aneurysms to be the result of incomplete resolution of embryonic vessels. Particularly the location of an aneurysm of the internal carotid artery to a point proximal to its bifurcation is better understood if the embryonic features of the vessels of the brain are considered.

It is, of course, clear that the material from different clinics will vary according to special circumstances. Jefferson in 1947 reported 158 cases of aneurysm of which 100 were located to the carotid artery.

The material presented in Table I is probably also deficient compared with autopsy material. The series published by McDonald and Korb (1939) showed a much higher percentage (21%) of aneurysms in the basilar and vertebral arteries.

It is well known that the great majority of aneurysms produce no clinical symptoms before they rupture. This is true of aneurysms in all situations other than the cavernous sinus. The clinical features of this group have been gradually outlined, especially by Jefferson.

The relation of the aneurysm to cerebral structures may give rise to other symptoms which might point to a definite location. These symptoms may be caused by local pressure or intracerebral hæmorrhage, the importance of which, from the standpoint of diagnosis, treatment and prognosis, is quite clear.

In Jefferson's series of 158 cases, neurological signs, other than ocular or oculomotor, occurred in only 7 patients. As shown in Table II hemiparesis, with or without aphasia, was a fairly frequent symptom in the present series and may occur with aneurysms in any situation. On the other hand the sudden onset of subarachnoid hæmorrhage simultaneously with hemiplegia or hemiparesis definitely points to an aneurysm of the middle cerebral artery. This occurred in 15 of our 23 aneurysms at this location.

The precise location cannot, however, always be foreseen, and the presence of an aneurysm may not be clear from the clinical features alone. Actually, the sudden onset of intracranial symptoms should always arouse suspicion of an aneurysm.

TABLE II.—SYMPTOMATOLOGY

	Number of cases	Hæmorrhage	Hemiparesis (aphasia)	Ophthalmoplegia	Migraine	Visual field defects	Trigeminal pains	Epileptic fits
Carotid art.								
Infraclinoid ..	9	2		8	7	1	6	
Supraclinoid ..	34	23	12	14	8	5	5	4
Carotid art. and bifurcation ..	2	2	2			1		1
Carotid art. and middle cer. art. ..	1			1	1			
Bifurcation.. ..	5	3	3	1	2	1		1
Proximal part of ant. cer. art.	8	8	3	1		2		
Ant. comm. art. ..	23	21	10	4		2		1
Distal part of ant. cer. art.	5	5	4			1		2
Middle cer. art. ..	24	23	19	3		4		1
	111	87	53	32	18	17	11	10

Angiography.

Angiography is necessary for the diagnosis and exact location of aneurysms and should be employed in every case suspected of vascular lesion. Sometimes aneurysms do not fill with contrast substance and in these cases encephalography might be helpful in localizing the lesion. The angiogram sometimes only indicates the presence of an expanding lesion. Angiography is not free from risks and complications but these are very few and do not influence the indications for angiography in these cases.

Angiographic studies should not be confined to the diagnosis and location of an aneurysm. Further information is necessary regarding the relation of the aneurysm to adjacent arteries, the existence and size of a neck, the state of the local and peripheral cerebral circulation and the adequacy of the collateral circulation of the circle of Willis.

Operative Measures.

The principal method of operative treatment for the intracranial aneurysms has been ligation of the carotid artery. We know that following internal carotid occlusion the systolic pressure distal to the occlusion falls to 50% and the pulse pressure to 25% of their initial levels. Therefore this procedure is probably of therapeutic value in the treatment of these lesions, by slowing down the circulation and assisting in the formation of a thrombosis in the sac and closing of the rupture.

Though ligation of the carotid artery is now considered a relatively safe procedure it is not, however, without risks. Post-operative impairment of the cerebral circulation might occur and produce transient or permanent hemiplegia or even death. Schorstein (1940) stated the opinion that the mechanism chiefly responsible for these complications was pre-operative impairment of the local or general cerebral circulation caused by the lesion for which the ligature was performed. This view was supported by Olivecrona (1944) in a study of ligature of the carotid artery in different conditions. Not infrequently the angiogram demonstrates, in addition to a reduced velocity in the cerebral blood flow, local abnormalities in the vessels surrounding the aneurysm. These are probably caused by vasoconstriction. Dandy believed that the cause of late signs of cerebral involvement was mainly thrombosis and embolism. Cases are reported in which this may be true but the influence of vasomotor impulses must also be considered (Fig. 2A and B).

Several methods of ligation have been devised for eliminating the risks of ligature, but it has not definitely been proved that one method is superior to another. It can only be said that some patients who do not tolerate occlusion of the internal carotid artery are able to do so if the common carotid is ligated first. We have always used just a single linen thread around the vessel followed, in some cases, by periarterial sympathectomy (indicated in Table III by figures within parentheses).

Post-operative Results.

The immediate post-operative results are shown in Table III. In only one case was the ligature not tolerated, necessitating its immediate removal. The patient who died, a woman aged 53, was

TABLE III.—IMMEDIATE RESULTS OF CAROTID LIGATION IN 37 PATIENTS WITH INTRACRANIAL SACCULAR ARTERIAL ANEURYSM

	Ligatures	Dead	Not tolerated	Transient hemiparesis	Transient hemiparesis. Removal of ligature
Common carotid art...	21 (1)		1	1	
Common and int. car. art.	12				2
Int. carotid	17 (9)	1		3 (1)	2 (1)

admitted following an attack of ophthalmoplegia with trigeminal nerve pains and paræsthesias. Angiography demonstrated an aneurysm in the cavernous sinus and ligature of the internal carotid artery was performed. The ligature was well tolerated but a few days later the patient complained of an increase in pain. According to Jefferson this is always a sign of activity in the aneurysm. Ten days after the operation the patient suddenly became comatose and died. Autopsy disclosed rupture of the aneurysm. It is difficult to say whether death was due to the ligature or not. Perhaps it is better to say that the ligature was unable to prevent fatal rupture of the aneurysm. The logical procedure in this case would have been to turn down a flap and place a clip on the artery above the aneurysm as soon as there was an increase in the trigeminal nerve pains.

Hemiplegia was transitory in all cases except one, a woman aged 28, who had an aneurysm on the left middle cerebral artery. Ligation of the internal carotid artery was followed by right hemiplegia and aphasia three days later. The ligature was removed but improvement was slow. Four years later, however, only a slight hemiparesis was present and the aphasia was minimal. In some patients signs of cerebral anoxia disappeared spontaneously and in others after removal of the ligature. It is therefore difficult to draw any definite conclusions regarding the value of removal of the ligature.

Late Results.

Published reports of late results are very few. Of Jefferson's 19 cases who survived ligature only one is dead seven years after operation from an unknown cause. All the others are alive and well. Krayenbühl reported 35 patients submitted to carotid ligation with a follow-up study in 14, none of whom showed recurrence of subarachnoid hæmorrhage. In Poppen's series of 101 carotid ligations there were 8 late deaths, of which 2 were presumably due to inadequate ligation resulting in a new rupture of the aneurysm. Table IV shows the late results in 31 of the 37 cases of carotid ligation in this series.

The fate of those patients who were discharged from hospital without any specific treatment is shown in Table V. Here the death-rate was comparatively higher. It is difficult to draw any positive

TABLE IV.—LATE RESULTS OF CAROTID LIGATURE IN 31 PATIENTS AFTER 1–14 YEARS

	Number of patients
Good, full working capacity	17
Epilepsy	4
Full working capacity	2
Mental changes	1
Hemiparesis	1
Mental disturbances	2
Dead from other disorders	2
Dead with signs of a new hæmorrhage	6
Verified rupture of the same aneurysm	2
Probable rupture of the same aneurysm	2
Verified rupture of another aneurysm	1
Cerebral hæmorrhage	1

TABLE V

Of 22 non-operated patients with saccular aneurysms verified by autopsy or angiography during 1935–1948 4 died in the hospital shortly after admission. Table V indicates the fate of the other 18.

	Number of patients
No reports	2
Dead from new bleeding (all within 3 years)	5
Dead from other disorders	1
Dead from unknown disorders	1
Alive up to 9 years after discharge	9
New attack of transient ophthalmoplegia	1
Persistent ophthalmoplegia	1
Disabled because of mental disorder	1

conclusions from such small series; it can only be said that in some cases carotid ligation is not adequate to prevent recurrent rupture of the aneurysm. Clinical experience shows that it is probable that the risk of recurrent hæmorrhage is reduced by carotid ligation if we take in account the high rate of recurrent hæmorrhages, recently demonstrated by Hyland (1950) in his study of the prognosis of the subarachnoidal hæmorrhage.

Prognosis.

I have seen no reports of a comparative study of the prognosis in verified aneurysms of different locations. Should there be a difference it would, of course, influence the indications for surgical treatment. I can give no figures to illustrate the point but I feel sure we have all seen cases of aneurysms in different situations in which death was due to hæmorrhage. Hæmorrhage is also the predominant sign in aneurysms of all locations except those from the subclinoid part of the carotid artery.

Our attitude to these lesions has been rather conservative owing to the fact that ligature was considered to be a relatively safe method and the intracranial attack was always considered a hazardous procedure. During the years 1932 to July 1950 aneurysms have now and then been explored, especially those rising from the anterior communicating artery in cases in which we felt carotid ligation would be of no benefit. In some cases the aneurysm was a surprise finding at an operation performed for

suspected tumour. In his monograph published in 1944 Dandy has outlined various methods for the treatment of an aneurysm by intracranial attack. Tables VI and VII show the location of our aneurysms and the type of operation performed.

TABLE VI.—INTRACRANIAL EXPLORATIONS OF SACCULAR ANEURYSMS FROM 1932 TO JULY 1950

Localization	Number of patients	Dead
Carotid artery ..	5	1
Proximal part of ant. cer. artery ..	1	
Anterior communicating artery ..	5	2
Distal part of ant. cer. artery ..	2	
Middle cerebral artery	1	
Vertebral artery ..	1	
	15	3

TABLE VII.—METHOD

	Trapping				
	Intracranial	Between intracranial clip and ligature in the neck	Wrapping with muscle or gel foam	Clip on the neck or excision	Exploration
Carotid artery ..	1	2	1		1
Proximal part of ant. cer. art.				1	
Ant. communicating artery			3	1	1
Distal part of ant. cer. art.	1				1
Middle cer. art. ..				1	
Vertebral artery ..				1	
	2	2	4	4	3

In recent years a more active surgical treatment with intracranial exposure of the aneurysm has been advocated by some neurosurgeons. This attitude is based on studies of the prognosis in spontaneous subarachnoid hæmorrhage reported from various clinics during the last years.

In Sweden two years ago Ask-Upmark and Ingvar (1950) made a follow-up study of 138 cases of their own and 385 from the literature. They concluded that 60% of the cases of subarachnoid hæmorrhage died sooner or later from the lesion. Only 20% had a chance of making good recovery. The remaining 20% became invalids. Hyland in U.S.A. made a follow-up study in 1950 of 191 cases of subarachnoid hæmorrhage, of these 100 died within six months after the first attack; 70 had the fatal recurrence within two weeks of the initial attack.

This high percentage of early recurrence has also been stressed by Falconer and is of greatest importance in assessing indications for operation.

Spontaneous subarachnoid hæmorrhage does not, however, indicate an aneurysm and an aneurysm does not always give rise to subarachnoid hæmorrhage. But in 90% of cases subarachnoid hæmorrhage is caused by an aneurysm and if the infraclinoid aneurysms are excluded about 85–90% of all aneurysms cause subarachnoid hæmorrhage.

Other clinical signs that might influence the indications for operation are pain in the distribution of the trigeminal nerve and visual failure due to pressure on the optic nerve.

Several factors, chiefly the poor prognosis in subarachnoid hæmorrhage and the fact that carotid ligation does not prevent a new fatal rupture of the aneurysm, have made us change our attitude toward these lesions. In August 1950 it was decided that in the future an intracranial exposure would as far as possible be made in all cases of intracranial aneurysms admitted. Ligature of the neck of the aneurysm was considered the procedure of choice and would be used whenever possible.

Location of the Aneurysm.

Tables VIII and IX demonstrate the location of the aneurysms and the method used. Of these

TABLE VIII.—INTRACRANIAL EXPLORATIONS OF SACCULAR ANEURYSMS FROM AUGUST 1950 TO NOVEMBER 1951

Localization	Number of patients	Dead
Carotid artery	11	2
Bifurcation of internal car. artery	4	1
Proximal part of ant. cer. artery	1	
Ant. communicating artery	14	
Distal part of ant. cer. artery	4	
Middle cerebral artery ..	10	
	44	3

TABLE IX.—METHOD

	Ligature of the neck	Wrapping	Trapping	Exploration
Carotid artery	9		1	1
Bifurcation	4			
Proximal part of ant. cer. art.	1			
Ant. comm. artery ..	11	2		1
Distal part of ant. cer. artery	4			
Middle cerebral artery ..	5	4	1	
	34	6	2	2

44 cases 23 have been operated on by the author and 21 by Olivecrona to whom I express my gratitude for permission to use his material in this study.

In 34 cases the neck of the aneurysm was ligatured, in 6 a strip of muscle was wrapped around the vessel, in 2 the aneurysm was trapped between clips. In one of the latter bleeding from the carotid artery occurred when attempting to place a ligature around the neck, necessitating trapping the aneurysm between clips which was well tolerated. In the other case a small aneurysm was found in the peripheral branch of the middle cerebral artery. The aneurysm was excised.

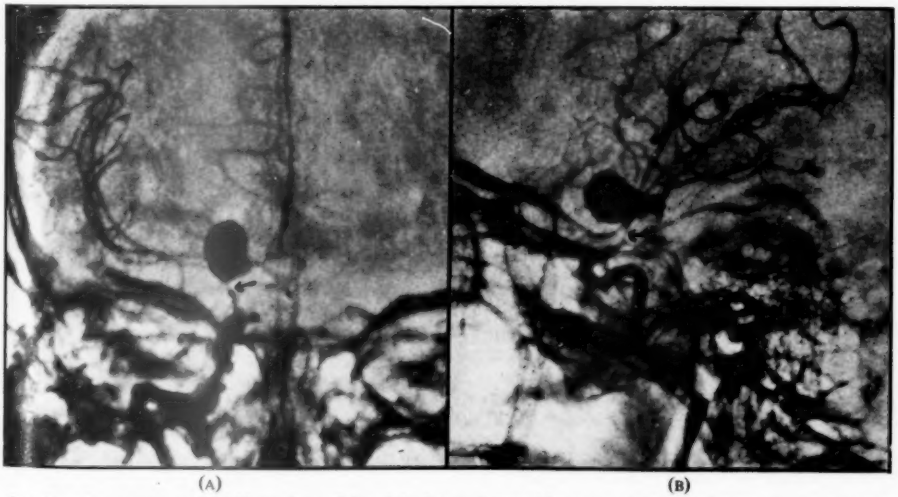
There were 3 operative deaths. In one of the cases death was due to the development of an extradural clot diagnosed and operated upon too late following successful ligature of the neck of the aneurysm.

The second was the only case which did not regain consciousness after the first attack of hæmorrhage. Emergency operation was performed during artificial respiration following respiratory failure. An angiogram had revealed a large aneurysm of the carotid artery. A frontal flap was turned down. The intracranial pressure was found to be very high and the subarachnoid space filled with blood. The frontal lobe was resected, digital pressure was applied to the carotid artery in the neck and the intracranial part of the artery exposed. Severe bleeding from the aneurysm necessitated temporary occlusion of the carotid artery with a clip. It was now possible to place a ligature around the neck of the sac and the clip on the carotid artery was then removed. The patient, however, died a few hours later. At autopsy a large rupture of the sac was found.

FIG. 1.—Aneurysm at the bifurcation of the left internal carotid artery.

The third case was a woman, aged 39, who had bilateral symmetrical aneurysms at the bifurcation of the internal carotid artery. She had lost consciousness after her first attack of subarachnoid hæmorrhage. On admission she was still drowsy, probably with signs of aphasia. She was observed for some days during which her condition fluctuated, one day more co-operative, another more somnolent. Nine days after the initial attack angiography of the left side showed an aneurysm at the bifurcation of the internal carotid artery (Fig. 1) and the following day an angiogram revealed an aneurysm of exactly the same location on the opposite side (Fig. 2A and B).

Immediately after this angiogram a left-sided hemiparesis developed and she became more drowsy. A stellate ganglion block was done and the hemiparesis cleared up. Close to the aneurysm on the right side the carotid artery as well as the anterior cerebral artery and the middle cerebral artery



(A) (B)

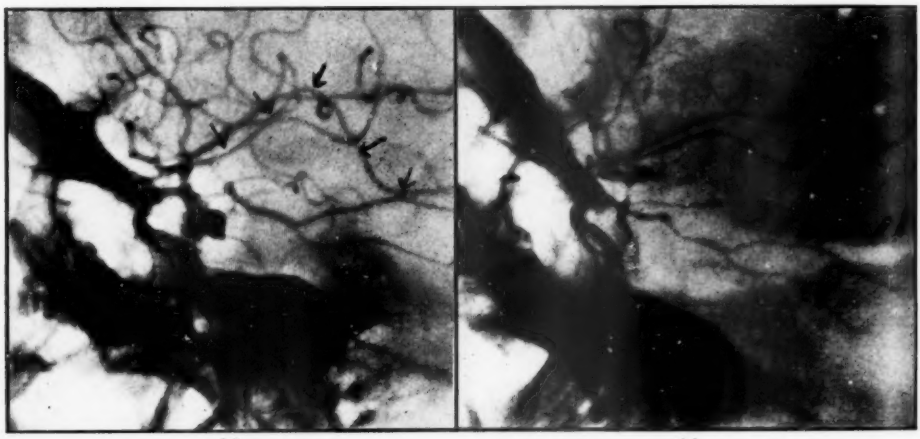
FIG. 2.—Aneurysm at the bifurcation of the right internal carotid artery. A, Frontal view. B, Lateral view. Note the vasoconstriction of the vessels close to the aneurysm, especially of the internal carotid artery just proximal to the aneurysm.

showed local vasoconstriction (Fig. 2A and B). At operation there was no difficulty in placing a ligature around the neck of the aneurysm, first on the right and then on the left side.

Shortly after the ligature was applied on the left side it was observed that the vessels changed their colour and size and became white and thin indicating pronounced vasoconstriction. At the same moment it was also noticed that the patient stopped breathing.

Presuming a reflex mechanism the ligature was removed and a clip was placed on the aneurysm slightly more distal to the main arteries. Stellate ganglion block and intravenous procaine were of no avail and the patient died the following day. Autopsy demonstrated that the ligatures were well placed around the neck of the aneurysms and the vessels had not been strangulated but were patent. No softening of the brain could be shown.

Other complications consisted of an extradural clot in one patient and post-operative brain œdema in another, both operated with success. 4 cases developed post-operative hemiparesis, one with complete recovery after stellate block, 2 with partial recovery and one became permanent. This last case, a woman of 46, was referred to the hospital after an attack of ophthalmoplegia and migraine. Angiogram demonstrated an aneurysm on the supraclinoid part of the right carotid artery (Fig. 3A).



(A) (B)

FIG. 3.—A, Aneurysm of the supraclinoid part of the internal carotid artery. Note the contrast filling of the posterior temporal artery. B, A clip is placed on the neck of the aneurysm. Note the absence of contrast in the posterior temporal artery.

At operation a clip was placed on the neck of the sac. In the afternoon the same day a slight left-sided hemiparesis was observed which increased during the following days to almost complete hemiplegia. There was no improvement in spite of the use of anticoagulants and sympathetic block. Angiogram three weeks later showed an occlusion of the posterior temporal artery in the Sylvian fissure (Fig. 3B).

In cases of aneurysm of the anterior communicating artery the study of the circulation of the circle of Willis by angiography is of utmost importance. In the present series the following variations were observed:

A. Filling of the aneurysm from both sides, 6 cases.

B. Filling of the aneurysm from only one side, 12 cases.

This latter group can be divided into two subgroups:

(1) In 3 cases filling of the aneurysm and anterior cerebral artery of the same side.

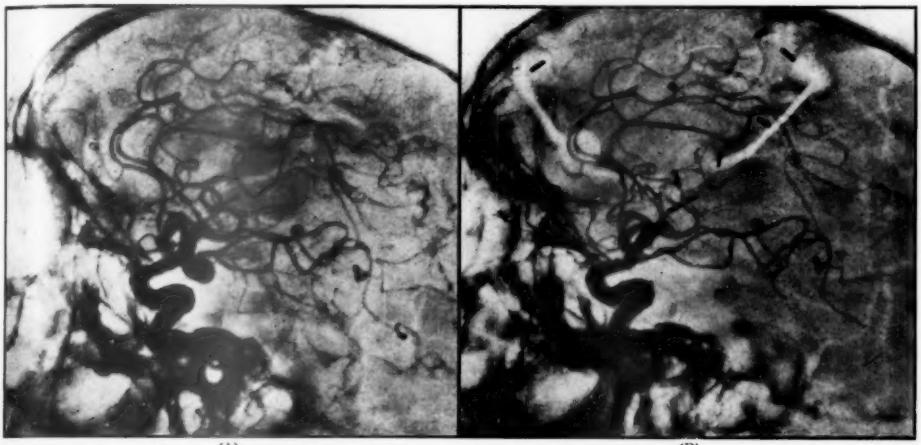
(2) In 9 cases filling of the aneurysm and both anterior cerebral arteries from one side. This group can also be divided into two subgroups: (*a*) no filling of the anterior cerebral artery from the opposite side, 7 cases; (*b*) filling of the anterior cerebral artery only from the opposite side, 2 cases.

We found that most aneurysms in this location, 10 out of 14, presented a neck suitable to ligation (Table IX). In one case only did the neck and the anterior communicating artery have to be ligated together.

In aneurysms arising from the middle cerebral artery ligation of the neck was not possible in 4 out of 10 cases and we had to rely on wrapping a piece of muscle.

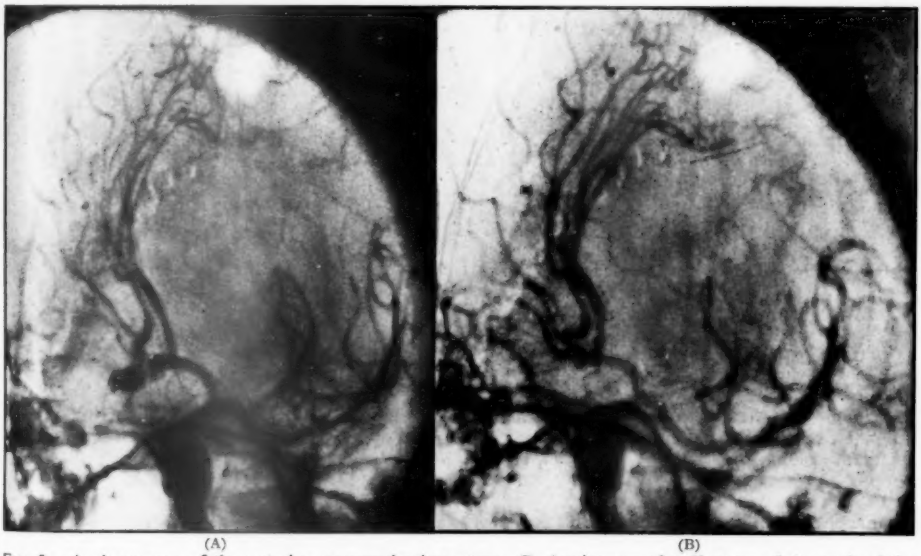
In 3 cases post-operative angiography showed that the ligature was not successful. The clip was not well placed or had slipped.

Figs. 4 and 5 show angiograms of 2 cases before (A) and after (B) ligature.



(A) (B)

FIG. 4.—A, Aneurysm of the supraclinoid part of the internal carotid artery with a very wide neck. B, Angiogram after ligature of the neck of the aneurysm with linen thread.



(A) (B)

FIG. 5.—A, Aneurysm of the anterior communicating artery. B, Angiogram after ligature of the neck of the aneurysm, with blood flow through the vessel preserved.

Summary and Conclusions

When an aneurysm is suspected angiography should be used not only to establish the diagnosis and to show the size and position of the aneurysm but also to demonstrate the presence of a neck, the influence of the aneurysm on the intracranial blood flow and vessels, and the adequacy of a collateral circulation.

Recent studies, in particular by Hyland (1950), have clearly demonstrated the high mortality rate in cases of subarachnoid hæmorrhage. The high percentage of fatal early recurrences has been especially stressed.

Ligature of the carotid artery in the neck has in some cases not been adequate to prevent a new fatal rupture of the aneurysm.

In a series of 44 consecutive cases of aneurysms admitted to the neurosurgical clinic from August 1950 to November 1951 efforts have been made to treat these lesions by direct surgical attack rather than by carotid ligation or conservative measures.

In 34 cases it was possible to ligate the neck of the aneurysm, in 6 muscle was wrapped round the outside of the aneurysmal sac, in 2 the aneurysm was trapped between clips and in 2 no definitive treatment was possible.

There were only 3 post-operative deaths. Hemiplegia developed after operation in 4 cases; in 1 this was permanent, in 2 there was partial recovery and in the fourth complete recovery.

Based on these preliminary experiences direct surgical attack must nowadays be considered a fairly safe procedure in intracranial aneurysm of any location except those in the cavernous sinus. Carotid ligature is not necessary as a preliminary step in these cases.

This paper is one of a series presented to Professor Herbert Olivecrona on his 60th birthday by friends and pupils. The author wishes to express his deep gratitude for constant help and encouragement and for experience gained under his leadership.

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Mr. Murray Falconer: My experience of intracranial aneurysms has been chiefly with lesions associated with intracranial bleeding. About 75 to 80% of cases of subarachnoid hæmorrhage are due to aneurysms that mostly are small. I have had little experience of the large lesions which, unruptured, simulate a brain tumour. Recently I (1950 and 1951) reported my first 50 cases of bleeding aneurysm submitted to operation with 9 deaths. These cases had been diagnosed by performing carotid arteriography in a group of 69 patients with subarachnoid hæmorrhage admitted consecutively to a neurosurgical unit in New Zealand, mostly within a few days of an attack of bleeding. The selection of these patients was not my choice, but was made by various medical colleagues who, either because they were alarmed at the condition of their patient or because of previous experience of surgical help, transferred their patient to the unit, usually without a neurosurgeon having seen him beforehand. Half the patients were experiencing recurrent attacks of bleeding and several were unconscious. Consequently, as a group, their prospects with conservative treatment were particularly serious. It is therefore gratifying that, in the aneurysm series, 33 patients made excellent recoveries (66%), while 5 recovered with a slight disability (10%) and 3 recovered with a severe disability (6%)—a total recovery rate of 82%. In the non-aneurysm series, there were 4 cases of arteriovenous malformation, 1 case of primary intracerebral hæmorrhage, and 14 cases with normal arteriograms. 2 of these last cases died, making 11 deaths, or an overall mortality rate of 16%, for the entire group of 69 cases of subarachnoid hæmorrhage.

Prognosis of subarachnoid hæmorrhage treated conservatively.—At first mention, these mortality rates of 18 and of 16% for surgically treated cases may sound forbidding, but they are an improvement on the results of conservative management, figures relating to which are available in the papers of Taylor and Whitfield (1936), Richardson and Hyland (1941), Magee (1943), Hamby (1948), Hyland (1950), and Falconer (1951). These statistics show that in most general hospitals between 50 and 60%

of patients admitted with subarachnoid hæmorrhage die, while only a sixth to a third of patients leave in a satisfactory state of recovery. The ultimate prognosis is even graver, for Hyland in following up a group of patients discharged from hospital an average period of 6·1 years earlier found that 20% of them had subsequently died of recurrent hæmorrhage.

One reason for this high rate is the marked tendency to recurrent bleeding. Between a quarter and a third of patients die within a few days of their initial attack, while subsequently half the survivors develop a recurrent attack, even while they are still in hospital. The incidence of these recurrent attacks reaches its peak from one to three weeks after the first attack, but the possibility of recurrence still remains for months and even years. Some patients experience several attacks. With each recurrence, the mortality expectancy rises higher. Consequently if neurosurgical treatment is to be tried, it should be undertaken preferably at an early stage before recurrent bleeding gets under way.

Value of early carotid arteriography.—Bilateral carotid arteriography is necessary to establish both the nature of the bleeding lesion and its precise site and size. It is therefore the first stage in the surgical management of subarachnoid hæmorrhage. For choice we carry out the procedure as early as the second or third day, certainly within the first week after onset of symptoms. The percutaneous technique is satisfactory provided an expert does it, but the test should always be carried out on the threshold of an operating theatre lest fresh bleeding is provoked. Examination of both carotid arteries is necessary because in about 10% of cases multiple aneurysms are present. It is also useful to investigate the collateral circulation through the circle of Willis. Thus if the carotid artery on the side of the lesion is compressed and the opposite carotid artery is injected, one can often demonstrate that this artery will supply both cerebral hemispheres. When carotid arteriography has not disclosed a lesion, one often proceeds to vertebral arteriography a few days later.

In my experience arteriography will reveal an aneurysm in about 75 to 80% of cases of subarachnoid hæmorrhage, an arteriovenous malformation in about 8 to 10%, and usually no abnormality in the remainder. Often the presence of an associated intracerebral clot is indicated by localized displacement of cerebral arteries. Leaking intracranial aneurysms tend to occur at certain particular sites, and as these sites give characteristic angiographic patterns, the aneurysms may be classified on a regional basis as follows:

(1) On posterior aspect of intracranial internal carotid artery in relation to the posterior communicating artery, 38% of cases in my published series.
(2) At bifurcation of internal carotid artery, 8% of cases.
(3) On middle cerebral artery at first point of branching of artery within fissure of Sylvius, 20% of cases.
(4) On proximal portion of anterior cerebral artery, 4% of cases.
(5) On anterior cerebral artery in relation to the anterior communicating artery, 22% of cases.
(6) Distal course of anterior cerebral artery at point of branching of artery, 8% of cases.

Aneurysms can also occur on the vertebral-basilar arterial system, but they are not common, and my experience is still limited to a single case (Falconer, 1951). Aneurysms of the internal carotid artery within the cavernous sinus (infraclinoid aneurysms) have not in my experience caused subarachnoid bleeding.

Place of carotid ligation.—Once an aneurysm has been demonstrated, its surgical treatment depends largely on its situation. Two different methods of attack can be employed, a carotid ligation and an intracranial attack, and these can be used either singly or together. Carotid ligation is the sheet-anchor of treatment for aneurysms of the internal carotid artery itself, and for these lesions may be employed alone, but for aneurysms on the circle of Willis or on the distal cerebral arteries it is of much less value owing to the collateral circulation through the circle of Willis. Even with aneurysms of the internal carotid artery, carotid ligation alone may not be sufficient to prevent recurrent bleeding at a later date. This is suggested by the observation that, some months after ligation, the aneurysm often may still be demonstrated by performing arteriography of the opposite carotid artery, the aneurysm filling by reflux from the circle of Willis, although perhaps a little smaller than before carotid ligation.

Carotid ligation in the presence of subarachnoid bleeding carries an appreciable risk, as witness the figures of Hermann, Obrador and Dott (1937), Schorstein (1940), and Krayenbühl (1946), who between them reported mortality rates of from 25 to more than 50%. Death in many instances is largely due to the intracranial bleeding, but to this may be added an anoxic effect resulting from interference with the blood supply. Some workers, and I understand that Dr. Norlén is included among them, have tried to lessen the risk of hemiplegia by measuring the intra-arterial pressure distal to the trial occlusion of the carotid artery, and then proceeding to carotid ligation only if the distal arterial pressure is above a certain figure. I have not tried this method, but have relied on observing the effects of a trial period of occlusion of the artery for twenty to thirty minutes with a Crile's clamp, while it is exposed under local analgesia. My preference is to ligate the common carotid artery in two stages and then the internal carotid artery in a further stage. Even when this course is followed, a delayed hemiplegia will sometimes supervene.

In my published series 36 cases were treated by carotid ligation with 6 deaths; 20 of these cases, including 2 of the fatal cases, were also submitted to an intracranial procedure.

Place of an intracranial approach.—The intracranial approach allows of a more definitive treatment of an aneurysm, and although I do not think this approach should be applied as a routine, in most cases

it offers prospects of a more secure recovery to compensate for the added risks. In my published series an intracranial exposure, with or without preliminary carotid ligation, was undertaken in 34 cases with 5 deaths.

By means of a frontal craniotomy it is normally possible to expose an aneurysm of the internal carotid artery or of its anterior and middle cerebral branches without damaging or sacrificing any cerebral substance. Aneurysms of the middle cerebral artery are exposed by splitting open the anterior part of the fissure of Sylvius, and of the anterior cerebral artery by opening up the great longitudinal fissure. Often aneurysms in these two latter situations are associated with sizable intracerebral clots in the adjacent frontal and temporal lobes, and an essential part of the operative procedure is to suck out these clots which are acting as space-occupying lesions. On several occasions now, I have succeeded in reviving unconscious patients by so doing.

One of the risks in exposing an intracranial aneurysm is that it may burst while it is being dissected out. This has happened now and then, but I have always managed to control the bleeding with hammered muscle. One of the advantages of a preliminary carotid ligation is that, if the aneurysm should burst, the force of bleeding is less. Recently we have made some attempts at lowering the systemic blood pressure with the new sympathetic-paralysing drugs, but not without some difficulties.

Once the aneurysm is exposed, we can apply a variety of local measures, e.g. wrapping with muscle, clipping of its neck, trapping by occluding the parent artery on either side of it, diathermy cauterization of the sac, and even in certain favoured sites excision of the aneurysm itself. I have not yet tried Norlén's method of ligating the aneurysmal neck, which from his photographs seems very suitable for lesions with accessible necks. But it has its limitations, as when an aneurysm has a wide neck or is so closely surrounded by diverging arterial branches that it is not possible to place the ligature in position without including one or more of these branches. The method which, to date, I have found most generally practicable is that of wrapping pledgets of hammered muscle around the aneurysm. This method was first introduced by Professor Norman Dott (1933), and his patient subsequently lived for many years before dying of an unrelated illness. My observations confirm that this method is probably of permanent value.

Magnitude of problem of treating bleeding aneurysms.—Subarachnoid hæmorrhage and bleeding intracranial aneurysms are relatively common lesions. My experiences show that surgical measures can be applied to the great majority of cases of leaking intracranial aneurysm, and not just to a selected minority. I feel that in the years to come most cases of subarachnoid hæmorrhage will be admitted to our neurosurgical units for investigation and treatment. Judging from statistics derived from New Zealand, about a hundred cases of subarachnoid hæmorrhage occur per million of population each year, and about half of these die (Falconer, 1950).

If further and wider experience confirms the belief that these patients have better prospects with surgical treatment than with conservative management, the time will come when the number of patients with cerebral aneurysms seen in our neurosurgical centres will rival if not surpass the number of patients with brain tumour.

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Sir Geoffrey Jefferson: Any method of treatment stands or falls by its success or failure. We have now had in my own Service enough aneurysms (250) and have treated surgically enough of them (177) to have formed conclusions that give, at the least, a good working basis. The great majority have been treated by Hunterian ligature, i.e. by ligature of the common or internal carotid arteries or both in the neck. This has now been done in 142 cases and of these 12 died during the first six weeks, 6 of a second rupture within one month of ligature, 4 were *in extremis* and probably should not have been operated on at all, 1 died of rupture of a second unsuspected aneurysm on the vertebral artery, and 1 died of basal compression by a large aneurysm. In no case could the death be related to the ligature itself, the patients died in one way or another of their aneurysms, i.e. by intracerebral clots or lacerations caused by bleeding or by irreversible damage to the anterior hypothalamus and "visceral brain".

There were 8 late deaths, 3 known to have been from hæmorrhage. Of these 1 died six years later from multiple aneurysms on the other side, 2 died from a rupture of the original aneurysm two and six years respectively after ligature. One died from a vast suprasellar aneurysm in which the wrong carotid had been tied five years before: there was no leakage here, it was the mass that was eventually fatal. The rest died from causes unconnected with the aneurysm. Perusal of these figures shows that if we omit the leaks from concurrent aneurysms on the opposite carotid tree or vertebral artery

we have to record 8 cases in which the same aneurysm bled again in spite of the carotid ligature, but only in 2 so far, who survived the first month. 20 cases in all died from various causes after carotid ligature. To have alive 122 cases, some many years old now, indicates to me that the method is one that has, to put it soberly, considerable merits.

I have to ask myself whether all these cases are safe. I cannot say that. The presence of an aneurysm is a serious thing and no absolute forecast can be made of the future of many of them. But we do not yet know how secure those patients are who have had direct attacks made on them (35, of whom 5 died promptly). And we have to remember above all that a certain number of aneurysms are quite impossible problems for direct attack. It would take too long to illustrate this most important pathological point in detail but there is still one thing to which attention must be drawn, namely, the neck of aneurysm. This neck is too often a radiological appearance and not an anatomical reality. All or nearly all aneurysms are sessile and spring from a considerable segment of the length and the total circumference of the artery. Often, it must be that the surgeon who records clipping or tying the

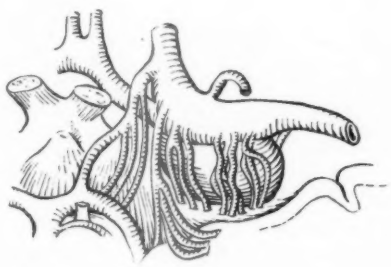

FIG. 1.

FIG. 1.—Middle cerebral aneurysm. Observe absence of "neck" and proximity of perforating arteries likely to be occluded by encircling ligature.

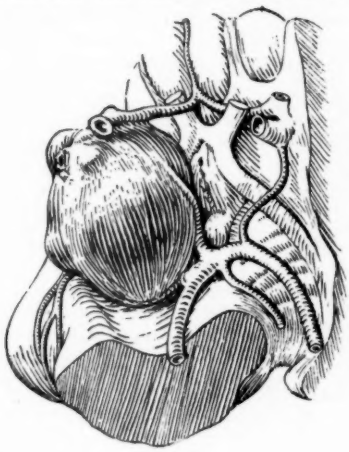

FIG. 2.

FIG. 2.—Aneurysm of internal carotid at origin of posterior communicating artery. Note wide base of origin—no "neck".

"neck" is constricting the aneurysm distal to its exact point of origin, as indeed Norlén has just shown in some of his post-operative angiograms. Whether this, none the less, confers immunity from further bleeding, time alone will show. It is for this and other reasons that one must demand an exact statement as to the real point of ligature in all future records. The aneurysms that cannot be treated by carotid ligature are those of the anterior cerebral where the aneurysm has been shown by bilateral angiography to fill equally well from both sides. The middle cerebral group occupies a middle position, for even though we may not be very satisfied with carotid ligature, everyone who has dissected them out knows that few can be dealt with locally by clipping, and that a ligature cannot be tied round them without including the branches of middle cerebral supply.

My colleague, Mr. Richard Johnson, will speak of the effects of ligature on the carotid circulation.

Mr. Richard Johnson: We know that proximal carotid ligation almost invariably reduces the size of aneurysms on the circle of Willis; the evidence is (1) clinical improvement in local signs, where present; and (2) visualization by angiography of an aneurysmal sac much reduced in size following ligation. There is also some evidence that ligation reduces the risk of subsequent leakage, although we have shown that it is not an absolute safeguard against further rupture, especially in the acute stage. About half the patients in this series had aneurysms which had leaked and in 29 cases the carotid was ligatured within a few hours of a severe hæmorrhage; 17 of these patients survived to be discharged from hospital and of these only 2 have since bled.

Ligation quite clearly has definite indications; it is sometimes an extremely valuable method of treatment in the very large aneurysms of the circle, which plainly offer no encouragement to a direct attack; and it is, furthermore, extremely effective in the treatment of infraclinoid aneurysms. Direct attack, on the other hand, is the method of choice for peripheral aneurysms which can be excised, or those which can be ligated (perhaps with the sacrifice of one or more relatively unimportant arterial branches). The best method of treating the small and moderately sized aneurysms of the circle itself (by far the largest and most important group) is not so apparent. Ligation may be of no value where there is free communication across the circle, or may be disastrous where the flow is inadequate, and yet our experience must mean that, between these extremes, it is for the most part effective. Exploration of the aneurysm, on the other hand, may be disappointing in revealing inoperability and carries a mortality and morbidity which at best is not very different from that of carotid ligation. Dr. Norlén's

impressive series demonstrates what advances in technical skill can do to render operable the great majority of basal aneurysms and it is doubtful if his results will ever be bettered. Eventually experience may determine clear indications for treatment, but at present it seems that for certain aneurysms, e.g. those in the region of the posterior communicating artery, carotid ligation and definitive surgery will have to stand trial side by side.

We attempted to solve some of the problems connected with the complications of ligature; the most serious is hemiplegia and in this series (150 cases) there were 11 instances, some transient, but 7 showing only that degree of recovery which one associates with a dense lesion. Some were slightly improved by removal of the ligature but there were no dramatic recoveries in the severe cases nor did sympathetic interruption affect them. Thrombosis or embolism in a main vessel would seem at first glance to be the most likely cause, but few observers have found these in fatal cases. Our evidence is that ischæmia, occurring either as a direct result of pressure drop in the vessels or as a result of a pressure fall allowing vessels stretched over an aneurysm to close down, is the cause in most instances.

For such reasons I commenced, some four years ago, to enquire in more detail what happened to the cerebral circulation when the carotid arteries were ligated in the neck. What effect did ligation have on the aneurysm (1) immediately, and (2) years later? What were the risks of carotid ligation, which carotid (common or internal) was it safer to tie, and which the more effective? These results were given in a Hunterian Lecture in 1950. In brief, the common carotid was ligated first, then, at various intervals, the internal was tied. At the second exposure an angiogram was made to show the sac and diodone was trickled into the common carotid and films taken to determine the direction of flow (demonstrated at the International Congress of Radiology, London, 1950). These investigations showed (1) that common carotid ligation reduced the size of an aneurysm, the fundus being partly thrombosed, and (2) that after an interval of six weeks or more the flow was from external to internal carotid, i.e. the external collaterals had opened up. Evidence obtained post mortem on 2 patients six years after ligation supported this: one after common ligation had bled from the same aneurysm; the other after internal ligation had bled from an aneurysm on the other side. It was apparent that after common ligation collaterals had opened up through the external and there was little difference in the calibre of the cavernous carotids of the two sides; the aneurysm, still large, had burst. After internal ligation, however, the carotid remained small up to its main branches and the aneurysm was shrivelled and fibrosed. Two years later we confirmed the work of Sweet and Bennett that common ligation reduced the mean carotid pressure by 40% to 60% and that although the external pressure was usually slightly higher than the internal, the difference was not great. We discovered, however, that in most cases after an interval of months, the external pressure rose as the collaterals opened up and that a further pressure drop could then be obtained by internal ligation. These results mean, in effect, that initially, common ligation is only slightly safer than internal ligation but that eventually internal ligation is more effective.

Sir Charles Symonds: Mr. Murray Falconer's conclusions concerning the mortality rate in patients with subarachnoid hæmorrhage who were not operated on were drawn from cases admitted to hospital and a considerable proportion of these patients were probably admitted because their symptoms were unusually severe. My experience suggested that many patients had subarachnoid hæmorrhages without being admitted to hospital at all. Therefore the prognosis for all cases of subarachnoid hæmorrhage not surgically treated was probably a good deal better than Mr. Murray Falconer's figures suggested.

Mr. D. W. C. Northfield: Dott and Adams McConnell were, I believe, the first to use muscle to pack around the aneurysm or in its cavity. I have operated upon a number of such cases, attempting a direct attack upon the aneurysm, in preference to carotid ligature. In those cases in which the aneurysm arises from the posterior aspect of the internal carotid artery close to the origin of the posterior communicating artery I have noted one point in its situation which I think is not usually perceived at necropsy. The sac may pass inferior to the sharp edge of the tentorium, and from the site of bleeding which has on occasion been encountered, it has seemed likely to me that spontaneous rupture may result from impingement of the sac on this sharp dural edge. In order to obliterate the sac, I have attempted to clip its neck; or have placed several clips across the sac itself. Where this has not been practical, I have surrounded the sac with a layer of muscle or of thin wisps of cotton-wool soaked in Thorotrast, hoping thereby to stimulate the formation of a barrier of firm scar. I have felt it important to prolong this packing over and around the parent vessel, much as a plumber "wipes" the T joint he makes with lead pipes. I have wondered whether ligating or clipping the neck may not still leave a weak area in the wall of the parent vessel, potentially another aneurysmal bulge. Reinforcing the aneurysm and binding it to its vessel of origin may possibly overcome this weakness. Reinforcement is also a method worth trying on aneurysms possessing several vital branches, provided one can adequately insinuate the material around it.

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Medical History at the End of the Nineteenth Century. To Commemorate Julius Pagel (1851–1912) and his Discovery of Mediæval Sources

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THE middle of the nineteenth century marks the transition from *speculative* medical history in the wake of "Naturphilosophie" (Kieser, Damerow, Friedländer and the revivers of the works of Paracelsus, such as Lessing and Preu) to *scientific* medical history (Adams, Littré, Daremberg, Choulant, Hecker, de Renzi, Rosenbaum, Haeser, Hirsch, Puschmann, Gurlt, Clifford Allbutt, Baas, Proksch).

Pagel's work as a whole.—Pagel's work, continuing the scientific tradition in medical history from the late eighties until 1912, is tripartite in scope. It includes the foundation of our knowledge of *mediæval medicine* based on his discovery of the original manuscripts, from which he produced the first edition and assessment of numerous mediæval sources; medical-historical *biography* and *bibliography*; and finally presentation of *historical subjects* and figures and of the *whole of medical history* (for detail, *see* Pagel, W. (1948), Victor Robinson Memorial Volume, New York, pp. 273–297, and Sigerist, H. E. (1951), *Bull. Hist. Med.*, **25,** 203).

(1) *Pagel and Medicine in the Middle Ages.*

General character of mediæval medicine.—The common view of the Middle Ages as a period of retrogression appears to be eminently applicable to medicine. The sixteenth and seventeenth centuries, with the foundation of modern anatomy, physiology and pathology, seem to continue where Galen (about A.D. 130) had stopped. Mediæval medicine contented itself with the aggregation, digestion and codification of the works of Galen and the reconciliation of apparent contradictions therein, the paramount method being that of formal logical hair-splitting, supported by astrology and almost juridical devices, such as the Lullian tables. Although thus concerned with the ancient sources, mediæval medicine is, in character, far remote from ancient medicine. The chief difference between them is not one of medical theory, which was the same in both (i.e. humoralism), but lies in the mediæval doctor assuming the rank and dignity of a *scholar* as against the ancient doctor, who had been a *craftsman*. Hence medicine and surgery, united in antiquity, separated largely because of the co-optation of the doctor into the ecclesiastical and scholastic hierarchy. The slogan: It is against the professional code for a doctor to use his hands—"Inhonestum magistrum in medicina manu operari"—epitomizes mediæval relegation of surgery to the ignorant barbers and quacks. Associated with this was the superadded sentimental, ethical and religious view of disease. Antiquity had regarded it simply as a natural process due to upsetting of the humoral balance by "too much" or "too little" therein. To the Middle Ages, disease was also fraught with the sense of sin as in the Old Testament or with the Christian idea of grace—ideas responsible for progressive and charitable institutions such as hospitals and isolation of the infectious but, at the same time, of necessity limiting surgical interference to a minimum.

Yet, the *spirit of observation and experiment was not altogether alien to the Middle Ages.* Physicians opposed the reckless application of moral theology to medicine and endeavoured to substitute natural for supernatural causes. There was an unbroken tradition in chemistry, derived partly from the exigencies of commerce and mining and partly from the aspirations of alchemy, as transmitted by

Christian, Gnostic and Neoplatonic syncretism with Oriental ideas. In this connexion, Arnaldus of Villanova and Roger Bacon must be recalled, as must also the proto-scientific element in "Magia Naturalis".

It was *surgery*, however, that formed perhaps the most direct and intense stimulus for observation, experiment and scientific reasoning in the later Middle Ages. This was not realized before the work of Julius Pagel.

Pagel's discovery of Mondeville.—In the late eighties, Pagel lighted upon the gap between the earlier Italian schools (notably Theodoric Borgognoni, 1206–1298), and the later stages of the schools of Montpellier and Paris (Guy de Chauliac, about 1290–1370). He closed this gap by his discovery, *editio princeps* and analysis of Henry de Mondeville (published 1889–1892. Nicaise's French translation—Paris, 1893—prepared from Pagel's edition is a useful secondary source which in no way excuses the scholar from referring back to the *editio princeps*).

Mondeville was born probably near Caen some time between 1250 and 1270. He studied presumably at Bologna and gave anatomical demonstrations at Montpellier in 1304. In these he used human anatomical situs figures and a human skull. He was surgeon to Philip "The Handsome", whom he accompanied to Flanders, while he went with Philip's brother, Charles of Valois, to Arras and England. He died after 1325.

Pagel's work established Mondeville more than any other mediæval surgeon as the prototype of the *scholar-surgeon*, who combined logical reasoning with keen observation and careful experimentation. This is evident in Mondeville's opposition to ancient and contemporary treatment of wounds and his institution of the *principle of antisepsis* (Pagel's edition, Berlin, 1892, page 137 *et seq.* *See* Pagel, Wundbehandlung im Altertum und Mittelalter. (1891) *Dtsch. MedZtg.*, **12,** No. 91).

The earlier school of mediæval surgeons, notably those at Salerno, believed that pus production would expedite wound healing, which should not be attempted by "first intention". Against this, Theodoric at Bologna had opened a new epoch. He had condemned interference with the wound and promotion of "laudable" pus formation (*see*, for detail, J. Pagel in the first modern and comprehensive representation of Medicine in the Middle Ages in Neuburger and Pagel's Handbuch der Geschichte der Medizin, Jena, 1902, **1,** 717). Mondeville, Theodoric's pupil, transmitted his master's message, which he put on an acceptable, rationalized, scientific basis.

Mondeville says: "The former method of dealing with wounds is faulty both in detail and as a whole: (1) because one probed wounds, (2) dilated them, (3) allowed them to bleed, (4) put in tents, (5) applied cold constringents locally, (6) failed to ligate properly, (7) promoted putrefaction, (8) violently removed fragments of bone from head wounds, and (9) ordered indigestible cold and humid food—methods which lead to much production of pus and fœtor with attending weakness, pain and danger for the patient and unnecessary labour for the surgeon" (Pagel's edition loc. cit. page 143 *et seq.*). Mondeville is definite and consistent on these lines, e.g. concerning the necessity of removing missiles, whatever the opinion of the public. For: "if he did not remove a missile from a wound, people will say: 'Master Henry is a man without compassion, for had he removed the missile the patient would have been cured.' If he did remove it and the patient lived, his reputation would not have been benefited for people would just say: 'Master Henry extracted the missile and the patient was cured or God has cured him', and had he died: 'Master Henry has killed him with his new cure and had he not removed it, he would be alive' " (loc. cit. page 153).

The same independent and progressive attitude of Mondeville is seen, for example, in the recommendation for the first time in medical history since Susruta of the *magnet* for the extraction of missiles (Pagel in (1897) *Allg. med. ZentZtg.*, **66,** No. 101, 1304 and (1898) **67,** No. 1, 11). Pagel's discovery of this was due to his shrewd interpretation of Mondeville's cryptic remark that there is still "another most reliable art of extracting missiles which cannot be described in words". That by this he really means the magnet is shown at the end of the work, where he says that it is the intrinsic and essential property—"tota perfecta species"—of the magnet by means of which it extracts a missile ("species, mediante qua magnes applicatus corpori extrahit ferrum infixum").

Mondeville's incisive remarks on medical deontology, on the intrigues of the physicians and the superiority of methodical surgery, reflect the struggle of the scholar-surgeon against the physician-schoolman on the one hand and the barber on the other. (Pagel (1892) *Dtsch. MedZtg.*, Nos. 14–17, 13, *see also* Sigerist, H. E. (1935) *Proc. Congr. Med. Educ.*, Chicago, pp. 73–74.)

Mondeville never finished his great "Surgery" probably prevented from doing so by long illness ("asma", "ptisis") and his extensive professional activities. Perhaps for this reason his sound principles, notably that of antisepsis, were soon abandoned. Guy de Chauliac, who succeeded him, acquired much more fame than his predecessor, though fundamentally inferior to him, as shown, for example, by his opposition to the principle of antiseptic treatment.

Chirurgia Jamati (*Jammaricius, Jamarius*).

A further discovery made by Pagel was the "Chirurgia of Jamarius", a Salernitan. This he found in a unique manuscript preserved in the Munich library. It had been missing for centuries and the *editio princeps* was published by Pagel in 1909. Its significance in the history of Salernitan surgery is now being appreciated and Pagel's early dating of Jamarius (twelfth century) supported (Holcomb,

L. C. (1944) *Bull. Hist. Med.*, **16,** 239). It is of particular interest that recently a second manuscript of Jamarius has come to light (first in Catalogue XV of Messrs. Feisenberger and Guerney, London). By permission of the Harveian Librarian and Dr. John Keevil, of the Royal College of Physicians, the present author is privileged to state that it is in the possession of the Royal College of Physicians and that it is contemporary and almost identical with the Munich manuscript edited for the first time by Pagel. It is at present being examined by Dr. Magda Pagel, who hopes to compile a report in the near future.

Conclusion

Pagel's work was thus instrumental in *revising the common view of mediæval medicine as a period of sterility and, indeed, of the "Dark Ages" at large*, more so than any other contribution to mediæval medicine that was made after him. This was largely due to the interest that Pagel paid to the *contents* of the sources, in addition to his careful literary analyses (*see also* on this point: Diepgen, P. (1951) *Berliner Med. Z.*, **2,** 353–355).

Short List of Sources First Edited and Analysed by Pagel

It is pertinent to append a short list of the main mediæval medical sources made accessible by Pagel's work.

He first edited the "Anatomy" by Henry de Mondeville (Berlin, 1889), one of the few sources of our knowledge of mediæval anatomy before Mundino. There followed the "Surgery" of William of Congeinna (Congenis)—Berlin, 1891—which belongs to the Salernitan School (Roger). The next works are Mondeville's great Chirurgia (1892—as quoted above), and the spurious surgery of Joannes Mesue jr. (Berlin, 1893) which, in its anatomical part, is probably Arabic in origin, and in its surgical parts dependent upon Saliceto, Bruno and the Antidotarium Nicolai. *Medical* texts include the works of Johannes de St. Amando, a Flemish canon belonging to the thirteenth century (his pharmacology—"Areolæ"—Berlin, 1893, and "Concordanciae" from Galen—Berlin, 1894). Further medical texts were those of Bernard Gordonius ((1894) *Pharm. Post*, **27,** pp. 205, 221, 235, 257). The treatise on eye diseases by Alcoatim, a Christian ophthalmic surgeon of the school of Toledo (about 1159) was published for the first time in 1896 ((1896) Neue Literarische Beiträge zur mittelalterlichen Medizin, Berlin, *see also* Janus, 1897, **1,** 371; 1900, **5,** 41; 1903, **8,** 530). The first edition of a Latin version of the "Surgery of Ali Abbas" by Constantinus Africanus ((1906) *Arch. klin. Chir.*, **81,** 735–786) has been of particular value for all students of Salernitan Medicine and Surgery. Pagel's last work, the *editio princeps* of the "Chirurgia of Jamerius" (Berlin, 1909) has been discussed above.

Little was added to the knowledge of those sources of mediæval medicine which Pagel had tackled for the first time. This was recognized by Sudhoff who said that Pagel's work on Mondeville "is the climax of his activities as a Historian and will always mark an epoch in the historical research in Medical History" ((1912) Beiträge zur Geschichte der Chirurgie im Mittelalter, Leipzig, II, p. XI). The additional information which Sudhoff had to offer concerned minor points (such as the possible origin of William of Congeinna in France, *ibid.*, p. 297). In addition, he replaced some of Pagel's conjectures by other conjectures. This is evident from a comparison of the preamble of Jamerius' Surgery with its wording in the new manuscript of the Royal College of Physicians. It also applies to Sudhoff's dating of Jamerius, *ibid.*, p. 391, as Holcomb has shown (*vide supra*). Sudhoff finally achieved hardly more than a shifting of emphasis in statements, the factual basis of which he could not deny (for example, the dating of the surgery of Salicetus—*ibid*, p. 412. This is commonly given as 1275. Pagel, however, discovered in it a case report dated 1280 and concluded that Salicetus had written his surgery after 1275. Sudhoff, however, preferred to assume that there are two versions of it, one more complete than the other; he surmises that the date is correct but that Salicetus added to his book later on).

(2) *Pagel, Medical History and Practice.*

The year of Pagel's birth—1851—saw the discovery of the ophthalmoscope by Helmholtz, the demonstration of the organ of Corti and the first construction of a sphygmograph, while Kölliker prepared his "Textbook of Histology" and Claude Bernard published the work on the function of the sympathetic nerve. It was a year of triumph for scientific medicine which, at this time, finally overcame "Romanticism" and "Naturphilosophie". Perhaps it was more than accidental that in this year the last "Naturphilosoph", Lorenz Oken, died. Pagel's teachers (1870–1875) were those men who led the tradition of Johannes Müller (1801–1858) and of Schönlein (1793–1864) up to a climax of scientific medicine: Du Bois Reymond (1818–1896), Virchow (1821–1902), Helmholtz (1821–1894), Traube (1818–1876), Frerichs (1819–1885) and Hirsch (1817–1894). Virchow and Traube and, in particular, Hirsch, were devoted to medical history and the moral which it has to teach. A child of his time and a pupil of these masters, Pagel was in his whole life actuated by a spirit of ethical pragmatism. He showed Mondeville as the harbinger of light in a "dark age" (1892). In his textbook of the "History of Medicine" (Berlin, 1898) with its first presentation of nineteenth century medicine, he inculcates the usefulness of medical history to medicine with arguments which are still being widely used and dis-

cussed (*see* Pagel, W. (1951) *Bull. Hist. Med.*, **25**, 207). In 1897, Pagel wrote a medical deontology based on historical considerations. However much purely academic work he had done, medical history remained to him something alive and capable of practical application. In spite of all the scientific discoveries which he had witnessed, he regarded the relationship between doctor and patient as being fundamentally unchanged since the times of the Hippocratic oath. Hence, to him the practitioner was to benefit most by medical history just as full understanding of medical history could only be derived from the professional activities of the doctor. This explains why he stubbornly adhered to his ideal of the practitioner-historian and, in spite of all temptation to drop a panel practice in favour of full-time academic activities, continued attending the poor and dejected in the slums of the Wedding district of Berlin.

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The Mid-Nineteenth Century Clinical School of Paris

By A. P. Cawadias, O.B.E., M.D., F.R.C.P.

The mid-nineteenth century was a great epoch in the history of Medicine. In Paris—the leading medical centre—great clinicians were developing the Hippocratic clinical approach to the patient and the Science of Nosology through the clinico-anatomical method. In Great Britain another group of great clinicians worked on the same lines, and parallel with them a series of great practitioners, based on a "common-sense" and empirical philosophy, were fostering the art of treating "the patient". In Vienna, Skoda, Rokitansky and their pupils were pushing to its extreme limits the Natural Historical method in the study of disease. In Germany an attempt was made to abandon the Hippocratic clinical approach in favour of a method based on laboratory procedures, and the nature of disease was being investigated. I shall attempt to study these cross-currents of medical thought and practice—so important for the understanding of our contemporary medical problems—by concentrating on the mid-nineteenth century Paris.

The Men

The triumvirate, Louis, Andral, Chomel, dominate the mid-nineteenth century medical Paris scene. P. C. Louis (1787–1872), a very conscientious observer, the introducer of the numerical method, has had the greatest influence on American medicine. Gabriel Andral (1797–1876), had a more brilliant intellect, and, apart from his clinico-anatomical researches, gave much thought to the ætiology and mechanism of disease, basing himself on extensive historical studies. Auguste-François Chomel (1788–1858) had the more comprehensive intellect, was a critic more than a creator, and through the elegance of his teaching and writings summed up his epoch.

Around this triumvirate was a whole galaxy of clinicians. Léon Rostan (1790–1866) allying precise clinical observations to courageous pathological thinking. Piorry (1794–1879) somewhat pompous, great exponent of the method of percussion. Pierre Rayer (1793–1867) a remarkable diagnostician and an authority on kidney diseases. Jean Baptiste Bouillaud (1796–1881), the Dr. Blanchon of Balzac's "Old Goriot", a colourful personality, a brilliant observer, but rather intempestive in his treatments. Armand Trousseau (1801–1867) the most eloquent and elegant of the Paris professors, principally a great teacher. Augustin Grisolle (1811–1869) one of the most objective clinical observers of the ages. L. Behier (1813–1876) great, principally as teacher, and one of the first to consider the constitutional factors in disease. G. B. A. Duchenne of Boulogne (1806–1875), probably the founder of modern Neurology, and forerunner of Charcot. To all these should be added the name of Pierre Bretonneau (1778–1862) who, although not a Parisian (he lived in Tours), had a great influence on the Paris school and is one of the foremost clinicians of all time.

All these physicians had some features in common which will help us to understand their work.

First, all of them were hospital physicians, and were enclosed in that special Paris Hospital system which does not resemble the hospital system in any other country. Students in Paris—and in France in general—enter the hospital wards from the first year of their studies. Even when they prepare for

what corresponds with us to the first M.B. they work in the laboratory and follow lectures on Physics, Chemistry and Biology in the afternoon but work in the wards the whole morning. Those destined for general practice will continue that daily hospital work for seven years. Those pursuing the high medical positions will continue to work in the wards and the pathological laboratory attached to the wards every day, often the whole day, until the age limit forces them to withdraw—one of the most heartbreaking events in the life of a French physician.

This exclusive and intensive hospital life explains the great clinical work of these physicians but also its limitation to the organic "hospital" diseases, and a certain therapeutic scepticism—of which Paris was freed only at the end of the nineteenth century, thanks to the vigorous personality of Albert Robin. Their contemporary British clinicians, less centred on the hospital wards could develop more the study of functional diseases and adopt a more courageous therapy.

Above all, these physicians had a great humanistic, cultural background, fostered by the French educational system with its stress on the classics, and by the brilliant intellectual environment of the mid-nineteenth century Paris, the Paris of Balzac and Victor-Cousin, of the great literary salons, of the cult of the intellect. In this brilliant society the physicians shone by their culture. In the course of one of his lectures Trousseau quoted some verses from Virgil and asked if anyone present could complete the quotation. A young, unknown student from Toulouse replied in flawless Latin. This was sufficient for Trousseau: He took the young man, George Dieulafoy, into his friendship, helped him in his studies, and made of him one of the most brilliant and eloquent clinical professors.

It was that great classical culture which gave these physicians that *esprit de finesse* so necessary for clinical observation, and the power of logic so important for scientific work. It was that same culture which gave them their great social influence, and the humanistic principles which we have inherited from the ancient Hellenes. "Woe to the day", wrote the philosopher Alfred Fouillée, "when physicians cease to constitute an intellectual élite".

The Hippocratic Clinical Approach

During the whole of the nineteenth century Paris was essentially Hippocratic, and the mid-nineteenth century accepted and developed the Hippocratic clinical method of approach to the patient.

There is much misunderstanding about the Hippocratic method, and most people think that it is purely a method of clinical observation. It is, in fact, much more than that. It is a method of medical reasoning based on the Platonic principle of knowledge "One in many, many in one", and applying the Platonic dialectic method. It should be remembered that Plato and Hippocrates were contemporaries and exercised a mutual influence on each other.

What is this Platonic-Hippocratic dialectic as applied to medicine? I have obtained an intuitive conception of my patient as a whole, and I proceed into the analytical examination of the parts. In the course of this exploration I encounter discrepancies between my first complete intuitive picture and the analytical findings, and this stimulates new enquiries upon the basis of which the picture of the whole is again modified. I continue the process of discovering new discrepancies and making new enquiries. . . . We cannot know the parts if we do not know the whole. We have to pass dialectically from the whole to the parts and from the parts to the whole with the object of a superior synthesis which is diagnosis.

The Hippocratic method was originally purely clinical, and as such it was developed by the mid-nineteenth-century French clinicians. Their wide culture, their artistic as well as scientific temperament, their humanism, their respect and sympathy for the human person which helped them to understand their patient—because there can be no understanding of a human being without sympathy—allowed them that intuitive vision and dialectic power which are the basis of this method. Their great talents of observation, fostered by intense work at the bedside and in the autopsy room, made them develop the clinical procedures of examination of parts, palpation, auscultation, percussion. The mid-nineteenth century Paris represents the zenith of the purely clinical method.

British physicians in the mid-nineteenth century worked on similar lines, and, in fact, there is a close parallel between the French and British schools of those days. Austria and Germany, however, adopted a different mode of approach to the patient. The Viennese, in particular Skoda and Rokitansky, had abandoned the Hippocratic spirit of the old Vienna school and were developing a purely local anatomical method of approach, their sole object being to determine the anatomical lesions corresponding to the patient's symptoms. The Germans rejected the Hippocratic clinical method and wished to understand their patients through laboratory procedures, which they were the first to develop systematically, and by fostering the conception of functional disturbances independent of anatomical lesion. (A conception due to Claude Bernard.)

As general methods of approach to the patient the Austrian and German methods failed. The Viennese "anatomical thinking" was too restricted, and resulted in a most despairing therapeutic nihilism. The German "rational physiological thinking" based on rudimentary laboratory methods, imperfect physiological knowledge, and ignoring the total reaction of the person, gave rise to errors

in diagnosis, to speculative physiological subtleties, and to dehumanized medicine. Austrian and German clinicians themselves repudiated at the end of the nineteenth century the ideas of their mid-nineteenth-century predecessors. However, the work of the Viennese and of the Germans was not lost, and combined with the Hippocratic method of the British and French gave rise to the Neo-hippocratic approach, combining the holistic and clinical reasoning of the Hippocratists with the laboratory procedures initiated by the German physiological school.

In this Neohippocratic method of approach (which reached its full development in the first years of the twentieth century, and particularly after the First World War) the first intuition of the whole is clinical, the study of parts is partly clinical, partly instrumental (laboratory). The ultimate synthesis is clinical. The dialectic passing from the whole to the parts and from the parts to the whole—the greatest act in diagnosis—belongs also to the clinician. As in the original Hippocratic method the whole includes the physical and social environment of the individual patient.

The patient is approached through clinical and laboratory medicine, (pathology, radiology, &c.): Both are indispensable, and, in particular, laboratory medicine gives us a precise knowledge of the parts. The last word, however, belongs to the clinicians, although, of course, this last word would be imperfect if the laboratory workers did not give us their invaluable help.

Nosology: The Natural History of Diseases

According to the teaching of the ancient Greek physicians as embodied in Galen the following is to be taken into consideration in medicine. A series of environmental factors act on a human organism, a Φὺσις and determine a disturbance of this organism, a πὰθος. This disturbance, this πὰθος, is manifested as a disease, a νὸσος, which we have to endeavour to treat. Hence, according to the Greeks, knowledge necessary for the practice of the art of medicine is embodied in four basic sciences, physiology, the science of human organism, pathology, the science of the processes of disease (the physiology of the sick as expressed by Magendie), nosology, the science of disease, of the manifestations of the disturbances of the organism and therapeutics. Much of our muddled thinking regarding the basic medical sciences would have been avoided by maintaining this clear conception.

Nosology is based on a special method of classification. The founders of this science, the physicians of Kos and Cnidos of the fifth century B.C., remarked that amongst the manifold manifestations of disease—symptoms and signs—there are some that occur in a regular mode of combination. They isolated these symptom-complexes and made of them morbid entities "diseases". These are, of course, artificial types but they are needed for classification of knowledge, and without classification knowledge is impossible. It is knowledge of these "disease-types", these "morbid entities" that allows us to approach the individual patient.

Nosology is, thus, the "Natural History of Diseases" as designated by one of the greatest nosologists of all time, Thomas Sydenham. It consists in the description of the onset, of the course, the termination of diseases, and of their characteristic features. Up to the end of the eighteenth century these described features were purely clinical, symptoms and signs. With the early Paris school anatomical features were added under the impulse of the work of Morgagni. With the late nineteenth-century French, British and German schools laboratory features were added under the impulse of the German mid-nineteenth-century physicians. Thus, Clinical Medicine, Morbid Anatomy and Laboratory Medicine contribute to the Natural History of diseases, or Nosology, but it is the clinician who rounds up the description. For this reason Nosology was called clinical science, but, unfortunately, this term has lately obtained another, and not so accurate, meaning. The description of the environmental factors which initiate the disease, that of the special personalistic features of those who are predisposed to that disease, and the modifications in the course of the disease brought by therapeutic and other factors belong to the Natural History of diseases.

The method followed in Nosology is the empirical method of observation introduced by Hippocrates and his contemporary Koan and Cnidian physicians, developed by the great school of Greek Empiricists in the last three centuries B.C., and applied with genius by Thomas Sydenham in the seventeenth century —under the influence of the empirical philosophy of Locke. The Paris clinicians adopted this method under the impulse of the positivistic philosophy of Cabanis, of Condillæ, of Auguste Comte, and advanced it into greater perfection. First they made away with the classification of diseases into general and species, classifications introduced by Boissier de Sauvages (1706–1767). Grisolle, in his standard work of mid-nineteenth-century Nosology, writes that classifications are not necessary, and that the most important factor is the precise isolation and description of the morbid entities, of the "disease".

Next, Louis introduced in this nosographical methodology the "numerical method", the statistical method, probably under the influence of Laplace and of other French contemporary mathematicians. Louis had a great influence on American Medicine, and when we read in American works of to-day that, for example, in a particular disease headache is encountered in 70% of cases, nausea in 50% of cases, and so on, it is an echo of the work of Louis. Our former president Dr. E. Ashworth Underwood has shown in a series of important papers how this numerical or statistical method applied

to Clinical Medicine first by Louis, has developed into a precise mode of exploration thanks to recent work, particularly that of Karl Pearson.

Last but not least these Paris clinicians perfected the clinico-anatomical method through prolonged observations and very careful autopsies. Hours were spent in noting all symptoms and signs in a patient, and hours in the autopsy room. Even in my own student days in Paris I have witnessed such painstaking work.

Following this perfected nosological methodology the mid-nineteenth century Paris clinicians made much progress in the study of natural history of diseases, but it would take too long to describe in detail their work on this point. The natural history of tuberculosis and of typhoid was studied through the painstaking work of Louis. Andral described the rheumatic conditions. Rostan worked on the thrombotic diseases of the brain. Grisolle gave a wonderful description of lobar pneumonia, Bouilland of rheumatic carditis.

The German mid-nineteenth-century clinicians rejected this nosology of the French, British and Viennese, and wanted to approach the patient directly through physiology and pathology. A great struggle went on but in the end the nosologists prevailed, and in Germany itself the late nineteenth-century clinicians rejected the principle of the Physiological school and adopted nosology as a basic science for the approach to the patient. As Naunyn the German wrote of Traube, "he too often made clinical medicine the servant of physiology losing himself in petty details and subtleties". It is true that "diseases" are artificial conceptions, but they are our tools for the approach of the patient, and we must perfect our tools.

Pathology (Physiopathology and Ætiology)

Although the natural history of diseases is the basic science for the approach of the individual patient it is not sufficient by itself. We have to answer the question, what is the disturbance of the organism that has determined these external manifestations, the disease, and what factors have caused this disturbance? In other words, we have to apply to our particular disease, or our individual patient, pathological (physiopathological) and ætiological knowledge. It is the knowledge of the intimate nature of disease that will help us to conquer it.

The French mid-nineteenth-century clinicians, however, avoided work on these lines as they realized the imperfection of physiological and pathological knowledge in those days. A few did pay some lip service to theories on the nature of disease, Andral, for example, developed the idea that a metabolic disturbance, a *vice de nutrition* preceded the organic localization, but on the whole physio-pathological conceptions were taboo. An early nineteenth-century Paris clinician, Gaspard Laurent Bayle (1774–1816) wrote: "We do not know the most important part of the laws that govern the human body in health and disease . . . We cannot penetrate the secrets which the Almighty seems to have reserved for Himself . . . But one can observe the signs of diseases, their symptoms, their evolution." Further, these clinicians had witnessed the disastrous effects of physiopathological speculations in history, and also in the person of their contemporary—an isolated doctrinaire—Broussais. The Germans, however, had not such scruples and loved pathological speculations . . . Schelling's Natural Philosophy was weighing hard upon them, and they reproached the French for their one-sidedness.

This was an age-long conflict. It was a repetition of discussions between Hippocratists and the λογικοί (the rationalists) around Diocles of Carystos in the third century B.C., a repetition of the battles between the dogmatics and the empiricists of the first century of our era, an echo of the vituperations of Sydenham against the chemiatrists.

The primacy of clinical observation—extended through laboratory methods—is the great lesson of the history of medicine. We cannot, however, limit ourselves to observation. We have to think about the intimate nature of disease, otherwise medicine will stagnate. Physiological and pathological knowledge are necessary and useful if controlled by clinical observation; and in the last resort they help the advancement of our science.

When Corvisart, Napoleon's physician, was describing to his Sovereign the method of the clinico-anatomical school Napoleon interrupted him, "And do you not leave a place for imagination . . . ?" Napoleon was probably right.

Conclusions

History in its original Hellenic sense means investigation, and is, in fact, the investigation of our actual problems in the light of the past. The study of the mid-nineteenth-century cross-currents brings us directly to the core of our contemporary medical problems.

The opposition between the Hippocratic clinical approach and the so-called Laboratory "rational" approach is encountered in our days, and it was even considered possible at one time to make a diagnosis by adding multiple laboratory tests. The Neohippocratic approach of the Mediterranean

universities attempts a synthesis between the two methods by maintaining the original clinical "holistic" approach, completed by the adjunction of laboratory and specialistic methods. Many recent papers, particularly in America (where it seems that a reaction against the mechanistic outlook in medicine is taking place) stimulates the recognition of the primacy of the clinic. Teaching, however, is as yet incomplete from that point of view, and students and young physicians seem to rely too much on laboratory tests. Is it because teaching is too much in the hands of scientific investigators instead of being in the hands of clinicians of wide culture, vision and comprehensive outlook, such as are considered the ideal professors of clinical medicine in Continental universities? Are we running the risk of being deprived of such clinicians as the Sydenhams, Laennecs, Oslers of the past, who received their training at the bedside, were developed in the observational school of medicine, and realized that the study of the whole man is the basis of our Art? The great development of laboratory methods and of specialism shows the importance of team work, but diagnosis remains, in the last resort, a process of clinical reasoning.

The opposition between the approach to the patient through nosology, or direct through physiopathology is again encountered in our days, principally regarding psychiatry and endocrinology. Psychiatrists speak of the rejection of the "Kraepelinean nosology" and of its replacement by a dynamic and individual approach. Endocrinologists have the tendency to press everything into physiopathological conceptions, hyperthyroidism, hypogonadism, hypercorticism, and so on, instead of isolating and well describing clinico-anatomical types—with their laboratory features. They seem to merit the reproach of Naunyn to the middle nineteenth-century German "rationalist", Traube, "The clinical pictures were recognized in so far they reflected physiological laws, and it was attempted to read the separate symptoms in the light of these distorted physiological images. Often one constructed them oneself instead of finding them by faithful and impartial observation". The recent trend, however, consists in recognizing that far from disturbing any individual dynamic approach a good natural history of diseases is indispensable. The pilot must know the rocks and narrows in his course.

The tension regarding the role of pathology—in the sense of physiopathology—is also being resolved. The mid-nineteenth-century French clinicians were right to be sceptical because in those days pathology was too much on speculative lines. To-day, however, thanks to the tremendous development of the experimental method pathology has given us a more precise knowledge of the disturbances of the organism and of their causes, and this helps us in our fight against disease. It has been accepted, however, that all physiopathological conceptions cannot have a direct application but should be controlled through clinical observation.

In fact history shows us that the solution of our contemporary medical problems lies in the primacy of the Clinic. Contemporary philosophy has turned away from the "Systems" and directs itself to the study of the concrete human being, and medicine is bound up with philosophy.

[*March* 5, 1952]

Arabic Philosopher-Physicians and Christian Doctors of Medicine

(A contribution to the knowledge of the origin of the Moslem revival of Science and the derivation of the Medical Profession)

By H. P. Bayon, M.D.

It can be assumed that serious and sound medicine, in the modern sense, began with the Hippocratic school and that the tradition has not been lost during twenty-four centuries, to the present day, notwithstanding the many aberrations due to astrological, alchemical or mystical fancies. Admittedly, Hippocratic medicine possessed a limited therapy, consisting of hydrotherapy, climatic treatment and gymnastics. It is therefore understandable that Galenism was welcome, with its many additional methods of treatment, which were modified according to the views of those practising the Healing Art.

It is, however, easily overlooked, that what we know as Medicine, is what has been recorded in manuscripts and printed books which, during many centuries, were the preserve of the mighty and the wealthy. Large portions of the population, both East and West, relied on home remedies and the ministrations of the "practical" leech, *medicus* or *hatibb*. It is only with the development of the

Hospital for the sick, some time in the fifteenth century, that all and sundry had the advantage of being treated by the learned physician or skilful surgeon, though even then many preferred the aid in disease of the unorthodox practitioner.

Thus the treatment of compound fractures or the grafting of amputated noses was performed in India by the potter's caste. In Southern Italy, in the fourteenth century, members of the Vianeo or Branca, of Catania, families grafted human tissues in a manner that was considered magical, hence the designation *Magia tropæensis*. It was only later that Gaspare Tagliacozzi (1546–99) of Bologna University recorded his method in print in 1597. Even then, grafting of surgical flaps was considered to be akin to magic—Tagliacozzi was buried in unconsecrated ground. Another surgical operation which was in the hands of skilled craftsmen in the West, together with the treatment of hernias, was the extraction of stones from the bladder, a common ailment and one which received the attention of travelling lithotomists. The names of the most renowned have been recorded—such as Pierre Franco (1505–70) or later on, the two Fransciscan Friars, Jacques de Beaulieu (1651–1719) and then Jean de Saint-Côme (1803–81): the latter, indeed, had the use of a private hospital.

In due time the orthodox profession took over these operations, together with the eye intervention for cataract; though "lens-couching" was performed in the market place in India and Egypt, within living memory.

In the transfer of the knowledge of ancient Hellas to later ages the libraries of Alexandria played an important part.

It is common knowledge that in buildings of cities, such as Alexandria, Constantinople, Rome, during the first five centuries of our era, the writings of ancient philosophers like Plato, Aristotle or physicians were preserved, even if neglected by the majority of Christian converts—if we except St. Augustine of Hippo (354–430). It must be admitted that the majority of the conversions to Christianity took place among the common people, who considered disease as a frequent retribution of sin and in most instances curable by Divine Intervention. This happened in the world of which we have coherent records and which can roughly be said to comprise the lands around the Mediterranean.

It is usual to accept that the light of Alexandria was dimmed after the death of Queen Cleopatra (69–30 B.C.) followed by the Roman conquest of Upper Egypt. Instead the intellectual importance of this city continued during five or six centuries, for Ptolemy the geographer, Galen the philosopher-physician and Plotinus (203–262) the Neo-platonist, flourished after the reign of Cleopatra. Soon Christians congregated in Alexandria and a Patriarchate was established, so that this seaport rivalled Rome as a fountain-head of Christianity. It is unfortunate to have to record that the Christian monks of Alexandria became notorious through gross intolerance and fanatical zealotry, having murdered Hypathia (370–415) the Neo-platonic woman philosopher. Cyril of Alexandria (d. 444) was Patriarch at the time and it is to be hoped that he had no part in this criminal outburst.

The libraries of Alexandria were famous and though on several occasions they sustained severe losses through fire and pillaging, it seems that they were replenished either by donations or the work of scholars. When the generals of Ibn al-Khattab Omar (assassinated 644) conquered Egypt in 641, it is said that all the MSS. were employed to heat the baths of Alexandria during six months.

It may be mentioned that Max Meyerhof (1945) translated the writing of one of the Jewish physicians of Saladin (1137–93)—Ibn Jami (d. *c.* 1180) who said that the MSS. of the libraries of Alexandria were not burnt, but were sent to Harran and Antioch for further study. Ibn Jami expressed the opinion that Christian kings were careless of ancient learning, which on the other hand Omar protected. In any case the destruction cannot have been very thorough for many of the works of classical times are known from survivals from the libraries of Alexandria.

For the proper understanding of the subject, it is necessary to recall some dates of general history, for now the so-called "Arabic" writers come into the picture. These wrote in Arabic characters, but only one was a true Arab, Al-Kindi (d. 873); the others were Moslems of different sects, some Jews and others Nestorian Christians.

The life of Mohammed (*c.* 570–632) is easily found in any Encyclopædia. He himself was not hostile to learning, for he is reputed to have said: "Science is twofold—Theology and Medicine." Even if this is a narrow assertion, it goes further than many of the statements of the Early Fathers of the Church, who opposed all pagan and worldly knowledge. Mohammed believed in the efficacy of drugs and had a Nestorian Christian from Jundi-shapur as physician; an example which later Khalifs followed.

In such matters, however, the opinions and actions of those who succeeded Mohammed are more important, for they show how his principles were put into practice. On his death, Abu Bekr became Ruler of the Islamic States, but he lived only a couple of years, from 632 to 634 and was followed in the Khalifate by a warrior, Abu Hafsa Ibn-al-Khattab Omar (assassinated 644) who, without leaving Medina, through his general, Abu Obeydah, organized the victories which brought under his rule the whole of Arabia, occupied Jerusalem, Syria, Armenia, Assyria and Mesopotamia. Alexandria and

part of Upper Egypt were conquered in 640. On his death, Omar was succeeded by Othman, son-in-law of Mohammed, who completed the conquest of Egypt and took Islam to Central Asia. Othman was assassinated in 656 so that the Khalifate passed to two claimants: Ali—a cousin of Mohammed, and Moawiya, a cousin of Othman. The adherents of these rivals were known as Shiites and Sunnites.

Moawiya and his Sunnites murdered Ali and removed the Khalifate from Mecca to Damascus, which had been captured by the Moslem, Khalid ibn Walid, and here, Moawiya founded the Ummayad Dynasty. From Damascus an unsuccessful attempt was made to capture Constantinople in 718, when, it is said, the Moslem ships were destroyed by "Greek fire".

Under the Khalif Walid—who reigned from 705 to 715—his troops resumed their conquering expeditions, invading Sicily, the Mediterranean shores of Africa and even entering Spain and crossing the Pyrénées into France, where they were defeated by Charles Martel (689–741) at Tours in 732.

The Ummayads however remained in parts of the Spanish peninsula and made Granada into one of the most splendid cities of Moorish Spain.

It will be easily seen that the Ummayads were mainly concerned with conquest and military matters; this is important because it might be easily concluded that the lively Moslem interest in classical learning flourished within five decades of the death of Mohammed. This is not so; it is the purpose of this lecture to suggest when and how the "Arabian revival of science" took place.

The Ummayads were supplanted by the followers of Abul Abbas, who founded Baghdad in 750 and transferred the Khalifate there. The Abbasids—as they eventually became known—were patrons of learning.

A pause must be made to consider the reasons that have been suggested for the sudden outburst of zeal in the translation of classical MSS. from Greek into Arabic.

It has been thought that this might be due to the inspiration given by Mohammed, whose recognition of learning was definite: indeed it might provide the reason why he tolerated the people of the Book (Christians and Jews) and was so unyielding in his dealings with Unbelievers or Khafirs. Others have mentioned the protection given and interest shown in all branches of learning by enlightened, even if tyrannical, rulers. This cannot be denied, for it is evident; what remains to be ascertained is: who were these patrons of learning? Again, the admiration for the rapid conquests of Islamic armies has been mentioned; but this would only explain the preference for Arabic script.

Partington (1937), p. 27, suggests that on reaching Alexandria, the Moslem conquerors in 641 found manuscripts explaining how to make gold, and to cure all diseases—accordingly they became interested and searched for further information. Against this it may be objected that the troops invading Alexandria were Ummayads and that the interest in classical learning began about a century later, not in Damascus, but Baghdad. Then the first writings to be translated from Alexandria were those of Aristotle and that the interest in astronomy originated in Persia. None the less, the suggestion is well worth considering, for it may provide a partial explanation of what is a most remarkable incident in the history of civilization. According to Guthrie (1945), p. 87: "Before the birth of Mohammed, however, the roots of Arabian medicine had been planted; planted, moreover, by an unorthodox but liberal-minded Christian." This can be accepted as a correct though restricted interpretation of events. For it must not be forgotten, after the first impetus provided by the Nestorians of Jundi-shapur, many other writers took up authorship, such as Persians like Rhazes, or Jews like Maimonides or Spanish Moors, such as Averroes.

The wanderings and vicissitudes of Nestorius (d. 451), Patriarch of Constantinople, condemned as a heretic by Council of Ephesus in 431—can be read elsewhere. What concerns us is that Nestorians, led by the Bishops of Edessa and Nisibis propagated their doctrines in Iraq, Persia, Malabar and China and in South-Western Persia, where in Jundi-shapur a school of medicine and dispensary or hospital were established, probably grafted on a Sassanian place of instruction. In this they taught the doctrines of Galen, on the basis of translations into Syrian.

It can be assumed that this hospital and school were functioning about five decades after the death of Nestorius, so that pupils could be taught. The renowned physician George Bachtishua of Jundi-shapur was the first of six generations of eminent physicians. It has been seen that a pupil of this school was physician to Mohammed.

The most renowned of the family was Gabriel Bachtishua, (d. 828-9) physician first to a Barmecide—a famous and wealthy family of Baghdad, who were massacred in 802 by order of Haroun al Raschid (763–809), with whom Gabriel became Court physician. He was one of the wealthiest physicians recorded in history, receiving fabulous sums for the cure of his masters and their favourites. In the end he fell out of grace with the Khalif, being imprisoned, and even condemned to death; however, he regained his former position with his successors, Al-Amin and Mamun.

His medical triumphs—as related by near contemporary authors—appear somewhat theatrical to modern eyes; consisting as they did in curing the, apparently hysterical, posture of a raised arm in a favourite of the Khalif by lifting her skirt, or bringing a dead man to life again by making him

sneeze. The splendour of his position at Court, the enormous fees Gabriel was paid, the fame obtained by his knowledge, all this would make him a worth-while example for ambitious youth.

Gabriel did not leave any writings; not so Hunayn ibn-Ishaq (809-73) known to the Latins as Johannitus, a gifted philosopher-physician, who translated nearly all Galen. He wrote medical treatises which, it is said, were bought for their weight in gold. Such reports would also impress young people and inspire them to follow in the path traced by these physicians. He lived under the protection of the Khalif Mamun (813–33) of Baghdad.

In the *Arabian Nights*, Vol. V, pp. 218–27, the story of the spendthrift Abu al-Husn and the clever slave-girl Tawaddud explains that the physician should not only be acquainted with Galenical medicine, but with theology, law, philosophy, astronomy, astrology, music and chess. The last is especially significant for it must mean that he could play with his patients; in other words was on a level with the mighty. Though the *Arabian Nights* often mention Haroun al Raschid, more probably, they were compiled in the twelfth to thirteenth centuries.

In any case they show that the philosopher-physician was a highly respected and learned person, very different from his Western prototype who, in the eighth century, was *nullæ litteris cognitus* or sat among the menials.

That concurrently with such sound philosopher-physicians, also quacks and charlatans existed is shown by Rhazes (841–926), who related how they cut the back of the head for epilepsy or extracted stones, lizards, worms by sleight-of-hand from their head, throat or elsewhere, (*On Impostors*, page 80, W. A. Greenhill's translation, 1848).

It is obvious that pupils from Jundi-shapur could claim superior medical knowledge obtained from Hippocratic or Galenical writings, but in the beginning of the Arabic interest in classical knowledge, astronomy was also included. This can be explained by the use of reckoning by the stars in making calendars; a knowledge which must have been obtained from the Persians. It is understandable that the wonderment aroused by the discoveries obtained in observing the firmament, the sureness with which certain celestial phenomena could be foretold or the results of seemingly miraculous cures, suggested that it might be possible to extend such triumphs to other spheres. This must also be remembered—Science was not as clearly defined as at present; in reading or examining some book on astronomy, chapters on optics or astrology might be encountered and an interest awakened in other matters.

The linking of astronomy and medicine by means of astrology was a process that began with Galen, but which the Arabic writers continued and extended, till by its neglect of anatomy and the symptoms of disease, it was a source of error and confusion.

Not so the compounding of drugs, which soon appropriated some of the methods of alchemy. Many of the manipulations of alchemy must seem a waste of time, effort and intelligence, yet it cannot be denied that the connexion with pharmacology and chemistry appears to have been continuous. The jargon of alchemy is not completely senseless; it can be interpreted in modern terms. Whether Arabic authors obtained their alchemy from India or from China cannot be discussed here. Though some medico-historians point out that no Arabic works of Geber are extant, yet it can be assumed that he lived in Baghdad in the eighth century and even if his original writings have not survived, the Latin translations with his name inspired many to follow his methods.

Summarizing, therefore, it might be said that the Moslem interest in the translation of classical manuscripts was mainly restricted to the Abbasid Dynasty and to the Ummayads when they were transplanted to Spain. It can be ascertained that, beginning with medicine and astronomy for practical purposes, attention was then extended to many other subjects of intellectual import, to which additions were made. Neither the mode of life nor the outlook of Hellas was adopted, for it was not a nation-wide concern, as art and literature were in Tuscany in the Medicean age or the fourteenth to seventeenth centuries.

It was previously suggested that the high esteem enjoyed by the philosopher-physician in Moslem lands may have inspired the authors of the Salernitan writings to style themselves "Masters of medicine". This designation, however, marked the distinction between the "*medicus*" or ordinary leech and those who not only could practise the Healing Art, but wrote treatises compiled from translations from the Arabic or, possibly, sometimes in the original Greek. At the time, "Master", "Doctor", "Professor" signified much the same—capable of teaching the subjects of the Trivium—Grammar, Logic, Rhetoric.

It can be asserted that it was from Salerno that the present-day medical profession arose, which by proving its worth, has become universal and can hold its own in practice and debate with any other system of Healing.

How the Salernitan writings were copied, recopied, modified, added to and eventually printed, need not be recalled. By means of its medical treatises, the fame of Salerno lasted longer than the actuality. In the time of Francesco Petrarca (1304–74) eminent teachers were no more.

Further developments can be clearly, or relatively accurately, documented—the gradual taking over

of medical education by the Universities or *Studium generale* as they were then called, the granting of the "Doctor's" degree, the acceptance of Arabic commentaries and translations of classical writings. Later on, direct and more accurate versions from the Greek were obtained following the scattering of scholars after the fall of Constantinople to the Ottomans in 1453. The eventual substitution of book-learning by direct observation, beginning with Andreas Vesalius (1514–64), then the dawn of experimental medicine in the seventeenth century with William Harvey (1578–1657)—all this is common knowledge.

While orthodox medicine was being transformed, popular or family remedies remained unaltered, though with the increasing effectiveness of academical medicine, home treatment has lost a great deal of its popularity. Even so, every busy medical practitioner will know of instances where rheumatism has been "cured" by carrying a potato in the pocket.

It may be asked: What remains of the Arabic revival? Apart from the numerals and numerous verbal survivals like alcohol, algebra, etc., it can be noted that several useful pharmaceutical technical manipulations, such as the extraction of vegetable agents, have an Arabic origin.

If it is required to know why the active interest in classics ceased nearly as suddenly as it originated, then it may be suggested that this coincided with the time when Latin translations of Greek classics became available through Niccoló Leoniceno (1428–1524) and Thomas Linacre (1460–1524). Printing hastened the declension which had already begun, when it became easier to learn what actually had been taught by physicians of the Hippocratic and Galenical Schools. This relates to the West; in the East, Avicenna is still consulted today.

In this essay, the fruit of reading during many years, it is far from easy to mention the authorities consulted. Exception must be made for: "Introduction to the History of Science" (Baltimore, 1927-1948) by George Sarton—which has proved invaluable, together with the "Encyclopædia of Islam" (Leyden and London, 1913-38), which afforded reliable information on political historical matters.

Dr. Douglas M. Dunlop, Reader in Islamic History, University of Cambridge, helped me greatly in providing information in relation to subjects about which I was in doubt.

The Wellcome Historical Medical Museum (Dr. E. A. Underwood) demonstrated important and rare Persian and Arabic MSS at the lecture, for which thanks are due.

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Section of Ophthalmology

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The Ocular Manifestations of Disseminated Sclerosis

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THE following observations on the ocular manifestations of disseminated sclerosis are based on a study of 91 cases of the disease. The cases selected are not chosen because they exhibit any special symptoms or signs referable to the eye, they are 91 consecutive cases of the disease which were treated as in-patients under the same Physician at the same Hospital. They are, therefore, representative of the general run of such cases.

I intend to refer in some detail to the changes which were found in the function of the pupil, but before doing so I should like to consider certain other ocular findings, and in the first place to deal with the visual symptoms of the disease.

(1) *Retrobulbar neuritis.*—A history of loss of vision of the type associated with an attack of retrobulbar neuritis was given in 25 cases, that is in 27% of those examined. In 8 of these cases the nerve involvement was bilateral, so that in all 33 eyes suffered from an attack of retrobulbar neuritis. In 4 of the bilateral cases the eyes were involved separately, but in the other 4 cases both eyes were involved together or within a relatively short space of time. In no case was there any evidence of the same optic nerve being attacked on more than one occasion. I do not know of any such case being recorded. Retrobulbar neuritis is not only a frequent occurrence in disseminated sclerosis, but it is often the earliest manifestation of the disease. This was so in 19 of the 25 cases recorded here. On the average the attack of retrobulbar neuritis preceded any other obvious symptom of the disease by eight years. The longest interval was twenty years.

In many of the cases which had suffered from retrobulbar neuritis there was a considerable degree of visual recovery as shown by the visual acuity recordings (Table I), but signs of permanent nerve damage were more readily detected by applying the Ishihara test (Table II), by examining the visual fields (Table III), and by studying the appearances of the optic discs (Table IV).

TABLE I.—VISUAL ACUITY IN 33 EYES WITH A HISTORY OF RETROBULBAR NEURITIS

$\frac{6}{6}$	14 eyes
$\frac{6}{9}$ to $\frac{6}{12}$	3 eyes
$\frac{6}{18}$ to $\frac{6}{60}$	8 eyes
Less than $\frac{6}{60}$	8 eyes

TABLE II.—ISHIHARA TEST IN 25 EYES WITH A HISTORY OF RETROBULBAR NEURITIS

Read correctly with ease	9 eyes
Read correctly with difficulty	2 eyes
Read with a few red-green errors	3 eyes
Complete inability to interpret numbers	11 eyes

(Ishihara test not performed in the other 8 eyes)

TABLE III.—VISUAL FIELDS IN 33 EYES WITH A HISTORY OF RETROBULBAR NEURITIS

Normal	9 eyes
Central scotomata	7 eyes
Paracentral scotomata	4 eyes
Peripheral contraction	13 eyes

TABLE IV.—OPTIC DISCS IN 33 EYES WITH A HISTORY OF RETROBULBAR NEURITIS

Normal	11 eyes
Temporal pallor	11 eyes
General pallor	11 eyes

(2) *Diplopia.*—In 28 cases, that is in 31% of those examined, there was a history of double vision. In 14 of these cases the diplopia had been the presenting symptom of the disease preceding any other manifestation by an average of four years. In 12 of the cases there had been more than one attack of diplopia (Table V). On the average there was an interval of five years between attacks, but in a few cases in which the attacks occurred frequently there was only a short interval.

In this series there were 2 cases which had suffered from both an attack of retrobulbar neuritis and of diplopia.

TABLE V.—DIPLOPIA IN DISSEMINATED SCLEROSIS

One attack	16 cases
Two attacks	8 cases
Three attacks	1 case
More than three attacks	3 cases

(3) *Brickner's oscillopsia.*—This symptom was mentioned by only 2 of the patients. It probably represents a subjective awareness of nystagmus.

OBJECTIVE SIGNS OF THE DISEASE

(1) *Eyelids.*—Ptosis occurred in 2 cases, in both as a uniocular phenomenon. In one of the cases it was part of a total oculomotor palsy, and the ptosis disappeared when the oculomotor palsy cleared up.

(2) *Extra-ocular muscles.*—(*a*) Nystagmus: This was present in 57 cases, that is 63% of those examined. The nystagmus was of various types as shown in Table VI. I use the term ataxic nystagmus

TABLE VI.—NYSTAGMUS IN DISSEMINATED SCLEROSIS

Simple horizontal nystagmus	20 cases
Horizontal and rotatory nystagmus	4 cases
Horizontal and vertical nystagmus	5 cases
Partial ataxic nystagmus	12 cases
Partial ataxic and vertical nystagmus	2 cases
Ataxic nystagmus	6 cases
Ataxic and rotatory nystagmus	1 case
Ataxic and vertical nystagmus	3 cases
Vertical nystagmus	1 case
Nystagmus in primary position	3 cases

to denote the type of nystagmus described by Harris (1944). In this condition there is nystagmus on looking to the right and to the left, but only of the abducted eye. The adducted eye in each instance remains stationary, and there is, therefore, a dissociation in the movements of the two eyes. Certain cases showed an incomplete form of this nystagmus, the adducted eye taking part in the nystagmus although to a lesser extent than the abducted eye. I have called this "partial ataxic nystagmus".

(*b*) Ocular movements: These were abnormal in 9 cases, that is 10% of the series, as shown in Table VII.

TABLE VII.—ABNORMAL OCULAR MOVEMENTS IN DISSEMINATED SCLEROSIS

Slight limitation of adduction and convergence	4 cases
Marked limitation of adduction and convergence	2 cases
Some limitation of abduction	2 cases
Total oculomotor palsy	1 case

(3) *Corneæ.*—In 2 eyes there were a few old K.P. although there was no previous history suggestive of an attack of iridocyclitis. I should not have regarded this as in any way significant, but Sorsby (1951) mentions that iridocyclitis may be a not uncommon finding in disseminated sclerosis or in the relatives of those suffering from the disease. I have had no previous experience of any such association.

(4) *Fundi.*—(*a*) Optic discs: There was pallor of the optic discs in 23 cases (26%). 17 of these cases have already been considered because in these cases the pallor followed a typical attack of retrobulbar neuritis. In the other 6 cases, 4 showed temporal pallor of one optic disc and 2 showed temporal pallor of both discs, despite the absence of any history suggestive of retrobulbar neuritis.

In each instance there was some additional evidence of damage to the optic nerve fibres, such as slight depression of central visual acuity, incorrect reading of Ishihara plates, and some defect in the visual fields (either a paracentral scotoma or a slight contraction of the peripheral field). It would appear, therefore, that involvement of the optic pathways can occur without any subjective awareness of such involvement.

There is a considerable difference of opinion regarding the number of cases of disseminated sclerosis which show temporal pallor of the optic discs. In this series 10% of eyes showed some temporal pallor, but a much higher percentage has been recorded in many previous series. It is well known, however, that even a normal disc can show some degree of relative pallor of its temporal part, and it may be that in cases of disseminated sclerosis where there is an equal degree of so-called temporal pallor of both optic discs, but in the absence of any history of loss of vision, and with normal vision, normal Ishihara test and normal visual fields at examination, it is best to consider such discs as within normal limits.

(*b*) The retinal vessels: There was some localized sheathing of the retinal veins in 9 cases, that is, in 10% of the cases examined. The phenomenon was bilateral in all except one case. The sheathing occurred especially in the equatorial regions of the eye. In only one case was the sheathing extensive. Rucker (1945) has described the occurrence of sheathing of the retinal veins in disseminated sclerosis. It is, of course, an interesting finding in view of Putman's theory of the relationship of the cerebral venules to the lesions in the central nervous system in disseminated sclerosis.

Pupillary Findings

In this series of cases of disseminated sclerosis the pupillary findings were:

(1) *The size of the pupil.*—The mean apparent pupillary diameter of the cases was 4·6 mm. with the extreme limits ranging from 2·5 mm. to 7·5 mm. (Fig. 1). I have excluded from these figures 3

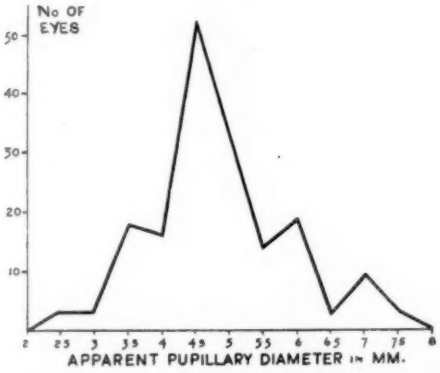

Fig. 1.—The range and frequency of pupillary sizes in disseminated sclerosis.

eyes examined during a purely temporary phase of mydriasis, 2 during an acute attack of retrobulbar neuritis and another examined during a total oculomotor paralysis. The mean figure of 4·6 mm. compares with a normal mean of 4·0 mm. It is doubtful if this difference of 0·6 mm. is significant, but at least it refutes, as far as this series is concerned, the idea that miosis is common in disseminated sclerosis. Adams, Sutherland and Fletcher (1950) in a recent series of cases of disseminated sclerosis also found that the pupil was larger than average in the majority of cases.

Anisocoria occurred in 11 cases. In 7 of them the amount of anisocoria was 0·5 mm., and in the other 4 cases it was 1·5 mm. The 3 eyes seen during the temporary phase of mydriasis are again excluded.

(2) *The occurrence of spontaneous hippus.*—The normal iris is never completely at rest even in a constant illumination, with the result that the diameter of the pupil is continually fluctuating in value. When these fluctuations are sufficiently large to be readily observed, the pupil is said to exhibit the phenomenon of hippus. Hippus, of an exaggerated type, has been observed in many cases of disseminated sclerosis. In this series I noticed obvious hippus in 33 cases of disseminated sclerosis, that is in 37% of the cases examined. In all except one of these cases the phenomenon was bilateral and equal on the two sides.

(3) *The reaction of the pupil to near vision.*—In only 2 cases of the series was there any apparent upset in the near reflex. In 1 case, one eye showed a slightly sluggish reaction to accommodation in association with a similarly sluggish direct light reflex. The other case showed a unilateral oculomotor palsy, and there was an absence of the accommodation reflex in the affected eye in association with absence of the light reflexes. This abnormal reflex was, however, only temporary, and the accommodation reflex became normal when the oculomotor palsy passed off.

(4) *The reaction of the pupil to light.*—There were 4 cases which showed a gross upset in the pupillary light reflex. 2 of the cases were seen during the acute phase of retrobulbar neuritis and in each instance the pupil was dilated and practically inactive to direct light. However, as the severity of the retrobulbar neuritis lessened and the vision improved there was a proportional return of pupillary function. The third case was one of a unilateral oculomotor paralysis. The light reflex was absent in the acute phase of the condition, but a normal reaction returned when the condition improved. The fourth case showed a partially developed Argyll Robertson phenomenon. Both pupils were small although equal in size. The direct and indirect light reflexes were poor, but the near reflex was brisk.

In addition to these 4 cases, however, there were 19 other cases in the series which appeared to show some slight upset of the light reflex as assessed by straightforward clinical tests. The direct light reaction was somewhat sluggish and ill-sustained in both eyes in 12 cases, and in one eye only in the remaining 7 cases. This deviation from the normal reaction was, however, difficult to be sure about without applying some more delicate test to the pupil. It was for this reason that I carried out in each case a test of pupillary reaction advocated by Stern (1944). He pointed out that a series of oscillations of the pupil could be induced by shining a fine pin-point beam of light just within the margin of the pupil. This induces, after a short latent period, a contraction of the pupil which cuts off the light from the retina. This is followed by dilatation of the pupil after another short latent period. The dilatation, however, allows the passage of light once more within the eye and the pupil again contracts. In this way a rhythmic series of pupillary oscillations is induced.

I have examined a series of cases by a similar method. Each patient was examined in a darkened room. The patient's head was fixed in a chin rest, and the eyes kept steady by instructing him to fixate on some point on the examiner's head, or on a point of light situated behind the examiner. Good fixation is an essential part of the successful carrying out of this test. A vertical focused beam of light from the slit-lamp was used to induce the pupillary oscillations. This differed from the point of light which Stern used, but the vertical beam appears to be equally effective in inducing the oscillations and it has the advantage that the character of the oscillation is more readily determined because of the increased general illumination. The oscillations were observed with the corneal microscope.

Three factors were recorded for each eye:

(*a*) The rate of the pupillary oscillations. This was measured by timing with a stop-watch the period taken for 30 complete phases of contraction and dilatation. In most cases more than one recording was made. The results were transposed into rate per minute.

(*b*) The amplitude of the pupillary oscillations was assessed arbitrarily as large, medium or small.

(*c*) The rhythm of the pupillary oscillations was observed for any irregularity.

In a series of 34 normal cases the mean rate of the pupillary oscillations was 62 per minute. The extreme values ranged from 50 to 77 oscillations per minute. The standard deviation for these rates was 5·9. The majority of the readings for the right and left eyes were fairly comparable. The mean difference between the right and left eyes was 3 oscillations per minute with a standard deviation of 3·2. The amplitude in the majority of cases was large. In a few cases the amplitude tended to decrease as the oscillations continued but this was generally due to a change in fixation, and full amplitude could be restored by altering the beam of light relative to the margin of the pupil. In all cases the rhythm was regular.

Campbell and Whiteside (1950) examined in detail the oscillations of the normal pupil induced by Stern's method. They made the interesting observation that the rate of amplitude of the pupillary oscillations is dependent to a certain extent on the basic size of the pupil. The smaller pupil was associated with a faster rate and a larger amplitude than the larger pupil.

This test of induced pupillary oscillations was applied to 90 of the 91 cases of disseminated sclerosis reported in this paper. One case was omitted because of continuous rapid head movements which prevented the test from being adequately carried out.

In the first place I shall report the results of 3 eyes examined during a temporary phase of pupillary upset. The two eyes which were seen during the acute phase of retrobulbar neuritis exhibited no true pupillary oscillations although the light produced "worm-like" contractions of the pupillary margin. The cases were, however, examined at weekly intervals from the onset of the neuritis, and it was interesting to follow the return of pupillary movement as the vision of the eye improved. At first the oscillations were slow and of small amplitude but later they became more normal. The third eye was examined during an attack of internal ophthalmoplegia, part of a total oculomotor palsy. Initially no pupillary oscillations could be induced, but as the severity of the ophthalmoplegia lessened slow pupillary oscillations of small amplitude were induced. Finally the oscillations became normal.

This leaves 177 eyes to be considered, of which 107 exhibited normal pupillary oscillations. The mean rate of the oscillations of these pupils was 61 per minute, with extremes of 51 and 86 per minute, and a standard deviation of 6·8. These results compare favourably with those of the normal cases already mentioned. In all cases the amplitude of the oscillations was of average extent, and the rhythm regular.

The remaining 70 eyes gave a seemingly abnormal response in one or more of the factors recorded.

The mean rate of the oscillations was 41 per minute with extremes of 9 and 75 per minute. The much greater scatter of rates is reflected in the standard deviation value of 12·5. There was an upset in the amplitude of the oscillations in these cases, and whilst the degree of upset varied considerably from case to case they can be grouped into different types. Firstly, in 48 of the 70 abnormal pupils the initial and sometimes even the next few oscillations were normal but there was a rapid tendency for the oscillations to become smaller and smaller in amplitude owing to a failure of the contraction phase. These small oscillations were superimposed, therefore, on a semi-dilated pupil. Secondly, in 20 of the 70 abnormal pupils the initial contraction was good but the dilatation which followed this was poor in extent and the subsequent oscillations were small—being superimposed on a semi-contracted pupil. Lastly, in one case both eyes showed a peculiar type of pupillary oscillation. The contraction and dilatation phases were full but they occurred in three or four slow, jerky stages, so that there was an obvious irregularity of rhythm.

Included in the 70 pupils which gave an abnormal type of pupillary oscillation were the 31 pupils which appeared, on ordinary methods of clinical examination, to have a somewhat sluggish reaction to direct light. This method of induced oscillations, therefore, confirmed in a more precise way a vague clinical impression. In addition it revealed an apparent abnormality in 39 other pupils.

The phenomenon of induced pupillary oscillations is an artificial pupillary reaction produced by creating a state which permits an alternating dominance of the sphincter and dilatator pupillæ muscles. The constancy of the phenomenon in normal subjects is evidence of the balanced co-ordination which exists between these two antagonistic muscles. The protagonist and antagonist are reciprocally innervated, active contraction of the one being associated with active relaxation of the other. Provided pupillary movement is not impeded by implication of the iris in any disease process, pupillary oscillations are dependent solely on the integrity of the light reflex arc. This reflex arc has an afferent and an efferent pathway.

The afferent pathway conducts light stimuli from the retina to the centres in the mid-brain. The efferent pathway has two components. First, a parasympathetic portion which supplies the sphincter muscle of the iris and produces contraction of the pupil. Second, a sympathetic portion which can be subdivided into two parts. There is a peripheral sympathetic tract which supplies the dilator muscle of the iris and produces dilatation of the pupil. There is also a central sympathetic tract which, according to Langworthy and Ortega (1943) supplies tonic inhibitory impulses to the parasympathetic pupillary centre and thus indirectly facilitates pupillary dilatation. Löwenstein and Levine (1944) have also emphasized the importance of the central sympathetic control, although they consider that an adequate central sympathetic tone is essential for complete pupillary contraction as well as for pupillary dilatation.

In 17 of the pupils in this series which showed an abnormal type of pupillary oscillation, there was some defect in the conduction power of the afferent pathways. This involvement of the afferent side of the light reflex arc may have been the cause of the ill-sustained pupillary response which was found in such cases. In the other cases, however, there was no detectable afferent lesion, and it may be that in these cases there was some upset, functional or organic, in the complex efferent pathways or in their related cortical or mid-brain centres, so that an imbalance occurred in the reciprocally innervated muscles of the iris.

I wish to thank Dr. Douglas K. Adams of the Western Infirmary, Glasgow, for allowing me to examine his patients, and for his interest and helpful advice during the preparation of this paper. I am also grateful to Professor W. J. Brownlow Riddell in whose department this investigation was carried out.

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Mr. F. A. Williamson-Noble referred to the appearance in some cases of a fine nystagmus which was observable with the ophthalmoscope. The eye appeared to oscillate in much the same way as a jelly wobbled on a shaky table. He had been introduced to this type of nystagmus by the late Leslie Paton, who called it "jelly-like" nystagmus. He agreed with Mr. Wybar that temporal pallor of the disc could be difficult to diagnose and that all one could be certain of was the difference between the colour of the discs in the two eyes. In order to estimate this it was important for the observer to use only one eye for examination of both the patient's eyes, otherwise the effects of pre-exposure came in. Another important point was to have the pupils dilated, examination through a small pupil frequently producing the illusion of pallor.

Sir Stewart Duke-Elder took up the point about comparing the two discs. He thought that much the best way to appreciate fine differences between two discs was the rather discredited indirect method of ophthalmoscopy in which one could look quickly and repeatedly from one to the other. He himself was apt to forget what one disc was like as he walked around the patient using the electrical ophthalmoscope.

Mr. Wybar said that several cases had monocular colour blindness, but in each case there was a history of retrobulbar neuritis or evidence of optic nerve damage.

The President agreed that persons with monocular colour-blindness might well be considered in this connexion.

Mr. Humphrey Neame supported Sir Stewart Duke-Elder in his advocacy of the indirect method in the examination of the optic disc.

Mr. Wybar, in reply to a question about the relationship between retrobulbar neuritis and disseminated sclerosis, said that it would appear that an isolated attack of retrobulbar neuritis in an otherwise healthy individual was most commonly a forerunner of disseminated sclerosis. W. J. Adie had seen a case in which the attack of retrobulbar neuritis preceded any other manifestation of disseminated sclerosis by twenty-four years. It was conceivable that the interval could be so prolonged that the retrobulbar neuritis might be the sole manifestation of the disease, and this was probably what Adie had in mind when he put forward the idea that disseminated sclerosis was the only known common cause of acute unilateral retrobulbar neuritis.

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President—Professor WILSON SMITH, M.D., F.R.S.

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SYMPOSIUM: THE DRUG RESISTANCE OF MICRO-ORGANISMS

Professor L. P. Garrod (St. Bartholomew's Hospital, London):

Acquired resistance to chemotherapeutic agents was first observed in trypanosomes, and can develop in other protozoa. Its occurrence in bacteria has come to the fore during the rapid therapeutic developments of the past sixteen years, and has sometimes been an obstacle to the successful use of sulphonamides and antibiotics. The capacity to acquire tolerance to noxious agents is by no means confined to microbes: indeed it appears to be a general property of living things. Flies can become resistant to D.D.T. and man to drugs such as morphia. Tolerance is most readily acquired to substances with a highly selective and special type of action, which necessarily includes any qualifying for use as chemotherapeutic agents. That any living thing should acquire a high degree of tolerance to a general protoplasmic poison is not to be expected, but it is well recognized that bacteria can alter to some extent in resistance even to phenol. It is on this account that regulations for conducting a phenol coefficient test require that the strain of *Salm. typhi* or other organism used should never have had any previous contact with the disinfectant.

The problem of acquired resistance as it affects the chemotherapy of bacterial infections at the present day may be stated shortly as follows: All species of bacteria can become resistant to sulphonamides, and resistance to one involves resistance to all. This change deprived these drugs of most of their value in treating gonorrhœa before penicillin took their place. Resistance was also observed although less commonly, and often only in special circumstances, in hæmolytic streptococci, pneumococci and staphylococci. It is interesting to speculate on what our position would be to-day but for the antibiotics: I have suggested elsewhere (Garrod, 1950) that we might well have been forced to return to serum for the treatment of pneumonia.

The usefulness of penicillin has been much less affected and no species has caused any serious trouble in this connexion except the staphylococcus. Most other bacteria, with the notable exception of Group A *Strep. pyogenes*, can be habituated to it in the laboratory, but except in individual cases treated for long periods this does not seem to happen in the body. There is no evidence of a general increase in resistance in any susceptible species except staphylococci: the comparison by Finland and his colleagues of the sensitivity of large numbers of pneumococci isolated in pre-penicillin days with that of recent strains is completely reassuring (Jackson *et al.*, 1950). Streptomycin is at the opposite extreme: all species can become highly resistant to it with unexampled rapidity, and by way of emphasizing how fragile a weapon this drug is they may also become dependent on it for growth. There is no doubt that permanent streptomycin-resistance is developing in bacteria generally throughout the civilized world: several authors (Romansky *et al.*, 1951; Chabbert, 1951) have noted marked increases in the frequency of resistant strains of various species, and most of us engaged in clinical bacteriology have noted the same thing. It is too early to say how far acquired resistance is going to interfere with the use of chloramphenicol, aureomycin and terramycin, but resistance to any of these drugs can be acquired (Foley *et al.*, 1950; Coffey *et al.*, 1950; Colquhoun and Weetch, 1950; Garvey *et al.*, 1950; Gezon and Finland, 1950; Meads *et al.*, 1950), and may embrace all three together.

In this brief clinical survey the mechanism leading to the appearance of resistant strains has been disregarded. It is certainly of two and possibly of three kinds. One is strain selection: the elimination, whether in the individual or the herd, of sensitive strains and their replacement by a few originally

resistant ones. No one disputes that this is what happened among gonococci with the sulphonamides, and it is strongly supported by the observations of Schmith and Reymann (1940) who showed that a small proportion of 50 strains isolated before these drugs had been introduced were resistant to them. We owe to Barber (Barber, 1947; Barber and Rozwadowska-Dowzenko, 1948; Barber *et al.*, 1949) the view, now generally accepted, that the same is true of penicillin and staphylococci. Here the argument is fortified by the fact that natural resistance and that produced by habituation have demonstrably different mechanisms.

These are not examples of acquired resistance, but only of selective breeding. In most cases, on the other hand, resistance in previously sensitive bacteria is a new character, and the way in which this change comes about has been a subject of violent controversy. The mutation hypothesis was first advocated by Demerec (1945, 1948) on the basis of experiments in which the number of cells resistant to penicillin or streptomycin was found to be more variable in separate cultures of the same organism than in multiple samples of the same culture. It certainly receives strong support from the recent work of English and McCoy (1951), who found that streptomycin-resistance in *Staph. aureus* was linked with capacity for growth in the absence of biotin, and obtained from a sensitive culture a non-biotin-requiring mutant which proved to be also streptomycin-resistant although it had had no contact with the drug.

The alternative hypothesis of adaptation has received strong support from the work of Hinshelwood (1944), who cites in its favour the exact correspondence sometimes existing between degree of adaptation and the drug concentration producing it, the phenomenon of multiple variation in which altered characters develop at different rates, and the appearance of variants in cultures derived from a single cell. An experiment of Abraham, Callow and Gilliver (1946) is highly significant in this connexion: they found that an organism rendered resistant to one antibiotic could be habituated to another with the same facility as the original culture. If the selection of mutants had been responsible for the first change, it is highly improbable that this process would have left any cells capable of the second.

Whatever the truth of this matter we should not, I think, be influenced by the argument that the adaptation hypothesis is contrary to the laws of heredity, in the sense that it involves the transmission of an acquired character. Until this argument was put forward, I confess it never occurred to me that these laws were applicable to bacteria, and I do not believe that they are. When an organism multiplies by simple fission, it would be surprising if any characters of the parent cell, however derived, were not also exhibited by the two new individuals so formed.

We need not assume that the mechanism of acquired resistance is the same for all toxic agents, or even for all antibiotics. There are strong reasons for regarding resistance to streptomycin as differing from any other, and it is here that the arguments in favour of mutational origin are strongest. Alexander and Leidy (1947) and many others have shown that a bacterial population may contain a minute proportion of cells originally and highly resistant to the drug, and they suggest that the outcome of treatment may depend on whether such cells are present. If this be true, the result of treatment should be predictable when it is possible to cultivate a large amount of the exudate in medium containing a high concentration of the drug. I have tried this in connexion with urinary tract infections, cultivating the deposit of 10 ml. of urine in agar containing 1,000 μg./ml. streptomycin, and the results, so far as they go, confirm that if more than very few colonies are obtained, treatment will fail.

What we need to know from the clinical point of view is how the emergence of bacterial resistance can be avoided. It is generally believed that exposure to inadequate drug concentrations tends to produce it. This may be due simply to insufficient dosage, and it would be useful to have some clear evidence that bacterial resistance is encouraged in this way. It may also be due to the nature of the lesion: tubercle bacilli in lung cavities are specially liable to become resistant, and I have several times observed an increase in resistance of the organism during the treatment of actinomycosis, possibly because of its presence in closed lesions more or less inaccessible to the drug.

Other aspects of this subject which merit discussion are the prevention of acquired resistance by the combined use of two drugs, and the effect of resistance to one drug on that to another. In the latter connexion there is unhappily a close relationship between the three newer antibiotics (Herrell *et al.*, 1950; Pansy *et al.*, 1950; Fusillo and Romansky, 1951). From the work of Kaipainen (1951) and Gocke and Finland (1951) it seems that cross-resistance is more marked and constant between aureomycin and terramycin than between either of these and chloramphenicol, and that both resistance to and cross-resistance between these drugs are more readily developed by Gram-negative than Gram-positive species. These authors have also brought to light another type of relationship: increased resistance to streptomycin or neomycin was accompanied by *diminution* in resistance to aureomycin, chloramphenicol and terramycin. A similar but still more remarkable finding (Chandler *et al.*, 1951) is that exposure to aureomycin of a penicillin-resistant staphylococcus abolishes penicillinase formation and renders it sensitive to penicillin. This change has been confirmed by Monnier and Schoenbach (1951) not only in *Staph. aureus* but in *Bact. friedländeri* and *Bact. aerogenes*. It remains to be seen whether this remarkable change can occur *in vivo*. We certainly still have much to learn about the behaviour of bacteria in relation to the newer chemotherapeutic agents, and as a clinical bacteriologist I confess to being somewhat daunted at the complexity and volume of the work which seem necessary in the individual case if treatment is to be intelligently directed.

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Dr. E. F. Gale (Medical Research Unit for Chemical Microbiology, Biochemical Laboratory, Cambridge):

The acquirement of drug resistance is easily demonstrated *in vitro*. A series of tubes containing a fully nutrient medium and serial dilutions of the drug is inoculated with a standard inoculum of a sensitive organism and incubated for a suitable time. At the end of that time the concentration of drug which has just prevented growth is read off. A similar series of tubes is now prepared and inoculated, not from the mother culture, but from that tube in the first series which contains the highest concentration of drug permitting growth. After incubation it will sometimes be found that the organism has grown in a higher concentration of drug in the second experiment than in the first, and the organism is said to have acquired resistance. The increase in resistance may be small or, in some cases, the organism may have acquired complete resistance and be able to grow regardless of the presence of the drug.

One reason for the acquirement of complete resistance in a single step would be the acquirement by the organism of the ability to destroy or inactivate the drug. This is known to occur in some cases of resistance to penicillin where the organism acquires the ability to produce an enzyme, penicillinase, which destroys part of the structure of the penicillin molecule and so inactivates the antibiotic. Some cases of the inactivation of chloramphenicol by metabolic processes have also been described.

Destruction of the drug is not the only reason for the acquirement of complete resistance in a single step. Such resistance is commonly described for streptomycin and there is no evidence that the streptomycin is destroyed by such resistant cells. We do not know the mode of action of streptomycin, or of any of the antibiotics used clinically, but some extremely interesting discoveries, which should lead ultimately to an understanding of its action, have been made by Umbreit and his co-workers (Oginsky, Smith and Umbreit, 1949; Umbreit and Tonhazy, 1949). If washed suspensions of a sensitive *Bact. coli* are incubated with pyruvic acid, a very small oxidation is observed; the suspensions are unable to oxidize oxalacetic acid at an appreciable rate but if both pyruvic acid and oxalacetic acid are presented to the organism together, then a rapid and linear oxygen consumption occurs, the oxalacetate apparently catalysing the oxidation of the pyruvic acid. If streptomycin at bactericidal levels is added to the reaction mixtures, it has little or no effect on the small oxidations of pyruvic or oxalacetic acids when present singly but abolishes the oxalacetate-catalysed oxidation of pyruvic acid when the two are present together. The explanation put forward is that oxalacetic acid and pyruvic acid combine to form a condensation product as part of a cyclic oxidation system similar to, but not identical with, the citric acid cycle known in mammalian cells. Streptomycin inhibits the condensation reaction and so prevents the cyclic oxidation of pyruvic acid in the sensitive cells. Similar experiments have been carried out with streptomycin-resistant mutants of *Bact. coli* and in these cells it is found that the oxidation of pyruvic acid is not affected by the presence of either oxalacetic acid or streptomycin. Therefore it would appear that the resistant cells effect an oxidation of pyruvate by an alternative path which does not include the condensation step and is consequently not affected by streptomycin. This then provides another means of acquirement of resistance: if the drug inhibits a single essential

step in the metabolism of the organism and the organism acquires, possibly by mutation, an alternative path which accomplishes the same reaction but which is not affected by the drug, then the organism will become resistant since its essential processes are no longer dependent upon the drug-sensitive step.

The work of the same team has also thrown light on the nature of the resistance to streptomycin of the cells of the host. They find that an oxalacetate-catalysed oxidation of pyruvic acid can be demonstrated in liver cells. If the reaction is studied in structureless, cell-free preparations, then the reaction is sensitive to streptomycin, but if the reaction is studied in intact cell or mitochondrial preparations, then it is not inhibited by streptomycin. One explanation of these findings is that the intact cells and the mitochondria possess walls or membranes through which streptomycin cannot pass and which, consequently, prevent it reaching the site of action of the sensitive enzymes. Investigations with isotopically labelled penicillin have demonstrated, similarly, that the yeast cell is not sensitive to penicillin since it possesses a wall through which the drug cannot pass. Theoretically, then, an organism can acquire resistance by a modification in the structure of its surface structures so that the drug can no longer enter.

If the drug attacks more than one essential system within the cell, then it is improbable that complete resistance will be acquired in one step. If one inhibitory action of the drug is short-circuited or prevented in some way, then the resistance of the organism will increase but only to the extent that that particular action is no longer effective, the growth still being inhibited by the action of the drug on other essential reactions. Thus if a drug attacks four separate but essential mechanisms in a cell, it might be expected that complete resistance would be acquired in four steps. That this is the case for the acquirement of resistance to sulphonamides in staphylococci has been shown by Oakberg and Luria (1947). They studied the acquirement of sulphathiazole resistance by a number of strains of *Staph. aureus* and found in every case that there were four or five well-defined steps in the acquirement of resistance on serial sub-cultivation. Consequently they suggest that sulphathiazole has four or five inhibitory actions in this organism.

The mode of action of the sulphonamides was clearly demonstrated by Woods (1940) who showed that these drugs competitively inhibit the essential metabolism of *p*-aminobenzoic acid and that there is a critical ratio of *p*-aminobenzoic acid to sulphonamide which determines whether growth shall occur or not. Consequently if the growth of an organism is just prevented by a concentration of sulphonamide, then the organism could overcome that inhibition if it were able to increase its production of the natural antagonist, *p*-aminobenzoic acid. Oakberg and Luria (1947) found that one of the steps in the acquirement of resistance was always greater than the others, and that this corresponded to an increase in the production of *p*-aminobenzoic acid by the organism. The other steps were not associated with such an increased production and must therefore have represented acquirement of resistance by other mechanisms.

A very large literature has grown up concerning the functions of *p*-aminobenzoic acid and its derivatives and it is known that this group of factors mediates the synthesis of certain amino-acids amongst other substances. One of these amino-acids is methionine and the acquirement of sulphonamide resistance is sometimes associated with a loss of the ability to synthesize methionine. Such resistant organisms cannot grow unless methionine is supplied in the medium and this growth is not highly sensitive to sulphonamides as one of the sensitive systems, i.e. that involving methionine synthesis, is no longer active. A specific form of resistance can therefore be acquired by loss of the enzyme system which is sensitive to the drug although this loss usually imposes more exacting conditions of growth.

Possibly the most complex process of acquiring resistance is that of resistance to penicillin. Bellamy and Klimek (1948) serially subcultivated a sensitive strain of *Staph. aureus* in increasing concentrations of penicillin and ultimately obtained an organism resistant to 4 mg. crystalline penicillin/ml. The progress of the resistance through some 64 sub-cultivations shows a number of ill-defined steps, indicating that penicillin has a number of inhibitory actions which have to be overcome. The nature of one or more of these steps has been indicated by our work at Cambridge (Gale and Taylor, 1947; Gale and Rodwell, 1949). *Staph. aureus* is an organism that, in the course of evolution, has lost the ability to synthesize a number of amino-acids which have consequently become nutritionally essential. We find that the organisms have acquired the ability to concentrate some of these essential amino-acids inside the cell in the free state before incorporating them into protein. This ability to take up amino-acids, such as glutamic acid, and concentrate them involves a metabolic process allied to a secretion and we find that cells that have been treated with penicillin have lost this ability to take up amino-acids from the medium. They use up the supplies already present within the cell, and growth then ceases since no more amino-acids can be drawn in from the medium. Primitive cells are able to synthesize their amino-acid requirements from ammonia and a carbon source, and are consequently not sensitive to the action of penicillin in preventing the assimilation of preformed amino-acids. We find that highly resistant staphylococci have also acquired this ability to synthesize their amino-acids from ammonia and a carbon source so that it appears that the organisms have acquired resistance by acquiring synthetic abilities enabling the cell to ignore the action of penicillin in preventing the use of preformed amino-acids. This would appear to be a special case of resistance acquired by an alternative path of synthesis short-circuiting the sensitive assimilatory mechanism.

In summary it can be said that research on the mode of action and acquirement of resistance to antibiotics and sulphonamides has revealed the following mechanisms of resistance:

(1) the ability to destroy or inactivate the drug;

(2) modification of the surface structures of the cell so that the drug cannot penetrate to its site of action;

(3) acquirement of an alternative metabolic path short-circuiting the path sensitive to the drug;

(4) increase in the production of a natural antagonist, or the substrate of the enzyme competitively inhibited by the drug;

(5) loss by mutation of the enzyme inhibited by the drug with consequent modification in the growth requirements of the organism.

Research on the mode of action of antibiotics is still in an elementary stage and it is highly probable that, as our knowledge increases, we shall find not only that there are other means of acquiring resistance but also that the suggestions put forward here are too simple to be true explanations.

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Professor R. Knox (Dept. of Bacteriology, Guy's Hospital Medical School, London):

There is one aspect of this problem of drug resistance in micro-organisms which has so far received little attention anywhere. The central problem, of course, is to explain how it is that micro-organisms become resistant. Is it by adaptation in response to the altered environment produced by the drug, or is it a selection of mutants in the population possessed of greater resistance than normal?

When we speak of enzymic adaptation we think of an essentially *homogeneous* population, in which *all* the cells react to the environment, in which the induced changes occur rapidly in the presence of the substrate, and may even occur without cell growth and often in washed suspensions of the bacteria without an added nitrogen source, and in which the adapted state disappears when the cells are subcultured in the absence of the substrate. In natural selection, on the other hand, we think of the *differences* within a bacterial population which contains for example a few cells much more resistant than the average, in which resistance of the whole population develops only as a result of selection of these more resistant members, and in which the resistance is genetically permanent and persists in the absence of the substrate.

There are many examples of both types of process occurring in micro-organisms. An example of the first is the adaptive system tetrathionase which we have studied—a system whereby organisms of the Salmonella group and some others are able to reduce tetrathionate to thiosulphate (Knox and Pollock, 1944). A clear example of the second type of process was provided by the work of Lewis (1934) who showed that a culture of *Bact. coli mutabile* which fermented lactose slowly in liquid media and which developed lactose-fermenting papillæ on solid media containing lactose consisted of predominantly non-lactose-fermenting cells but with a small proportion (about 1 in 10^6) of "mutant" cells capable of fermenting lactose. These cells were *present* in any culture of this organism but were *selected* only if the medium contained lactose.

The main point I should like to emphasize is that the two types of variation I have described are not to be regarded as coming from opposing schools of thought—the Lamarckists or Lysenkoists on the one hand believing in the inheritance of acquired characteristics, the orthodox geneticists on the other emphasizing natural selection—but that in many cases the two processes can be seen working together. In many examples of bacterial variation there are two factors: (1) The latent *capacity* to adapt, which is genetically permanent. (2) The *development* of that capacity in response to the environment. This is not genetically permanent.

It follows that a culture of micro-organisms would be unable to multiply and might even die, if incubated in conditions in which the development of an adaptive enzyme was a limiting condition for growth or survival. This has already been shown to occur with the adaptive system tetrathionase. The adaptive formation of this particular enzyme system is more sensitive to heat than the process of growth (Pollock, 1945), and so organisms which grow well up to temperatures as high as 42° C. when freely supplied with oxygen do not grow at 42° C. when oxygen is replaced by tetrathionate as hydrogen acceptor, because they cannot at that temperature adaptively produce the enzyme system without which they cannot utilize the tetrathionate (Knox, 1945, 1950).

Dr. Collard and I have recently shown that a culture of *B. cereus* behaves in the same way with regard to penicillinase production. A short account of this work is in the press (Knox and Collard, 1952), but the essential points are shown in Table I. It can be seen that after overnight incubation

TABLE I.—EFFECT OF INOCULUM SIZE ON GROWTH IN PENICILLIN BROTH AT 37° C. AND 42° C.

Penicillin concentration units/ml.	37° C.				42° C.			
	Inoculum diluted							
	1/1	1/10	1/100	1/1000	1/1	1/10	1/100	1/1000
0	+	+	+	+	+	+	+	+
1	+	+	+	+	+	tr.	tr.	0
10	+	+	+	+	+	0	0	0
100	+	+	0	0	tr.	0	0	0
1000	+	0	0	0	0	0	0	0

+ = growth, tr. = trace of growth, 0 = no growth.

at 37° C. large inocula of the organism grew well in penicillin concentrations up to 1,000 units per ml. and that small inocula grew up to 10 units per ml.: at 42° C. on the other hand, while large inocula grew in broth containing up to 10 units of penicillin, dilute inocula did not grow even in as little as 1 unit per ml. The organism, in fact, is inherently sensitive to penicillin, but is able to protect itself against the bacteriostatic, and perhaps also the bactericidal, effect of penicillin by means of penicillinase. At 37° the organism adaptively produces greatly increased amounts of penicillinase in response to penicillin (Duthie, 1944; Housewright and Henry, 1947; Pollock, 1950), and therefore it is able to grow in high initial concentrations of the antibiotic; at 42°, although previously formed penicillinase is highly active, the cells are unable adaptively to produce more of the enzyme. The result is that growth will occur at 42° only if the cells inoculated already contain enough penicillinase. This happens either if the inoculum is large or if it consists of cells previously adapted to penicillin.

There are two other aspects of the problem:

(1) *Interactions between different micro-organisms.*—It is evident that processes of the kind mentioned above may be important in determining the survival of different organisms in a mixed bacterial population. Production of penicillinase might at first protect only those cells which were actively producing it, but if a large quantity of extracellular penicillinase were produced, a wide "umbrella" of penicillinase might be capable of protecting other bacteria which were in themselves highly sensitive to the antibiotic.

(2) *Interactions between drugs.*—In considering the use of more than one drug at once, e.g. sulphonamides with penicillin, streptomycin with *p*-amino-salicylic acid, aureomycin with penicillin, etc., the following points would seem to be important:

(i) Mutants resistant to both drugs are likely to be very rare.

(ii) Where enzymic adaptation to one drug is essential for survival of a bacterial species, the presence of another drug might suppress any chance the cells had of forming an adaptive enzyme.

(iii) On the other hand we might expect in some cases to find a rather curious type of antagonism between drugs. It is well known for example that penicillin is most effective against actively dividing cells; if the addition of another drug prevented the bacterial cells from getting into a metabolic state in which they were vulnerable to penicillin, the combination of the two drugs would be less effective than penicillin alone.

We know far too little about the possible clinical effects of interactions between different drugs and micro-organisms but I think our understanding can only be increased by studying carefully the ways in which environmental and genetic factors may be interrelated. The bacterial cell cannot adapt unless it has the right kind of gene, and the gene is not of much use to the cell if conditions are such that it cannot adapt.

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